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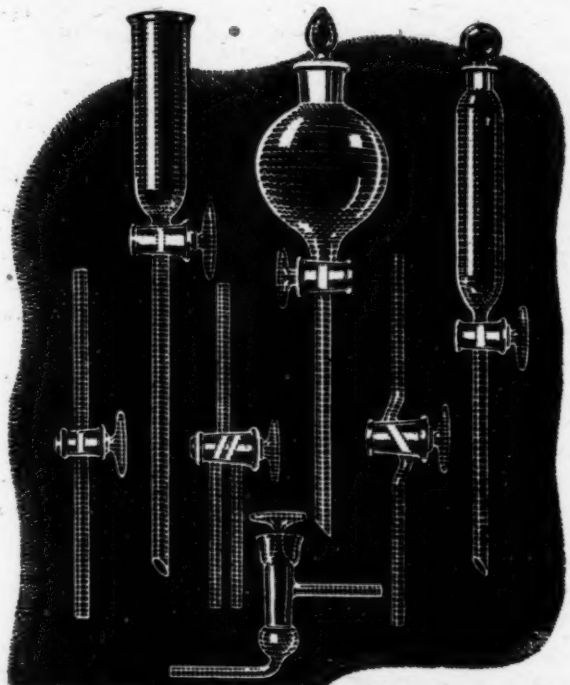

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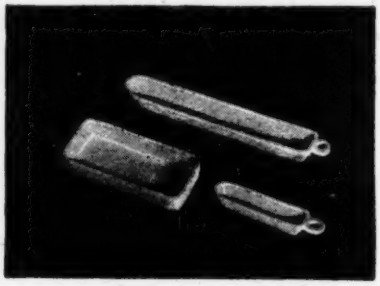

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position by iodide as given in the Sandmeyer paper and (2) the reaction above. The pyridine would thus appear to play the rôle depicted in (VII*a*) (*loc. cit.*, p. 774), *viz.*, formation of an ephemeral diazoamino-compound, which would retard reaction (2) and promote reaction (1), since in its absence the main product is 1 : 8-naphthasultone.

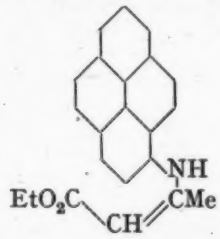
The authors cordially thank Prof. W. M. Cumming and Dr. F. G. Mann for their interest in this work.—TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, February 16th*, 1942.]

Derivatives of 1′-Aza-3 : 4-benzpyrene. By M. WEIZMANN and F. BOGRACHOV.

THE application of the Skraup synthesis to 3-aminopyrene (Vollmann and co-workers, *Annalen*, 1937, **531**, 52) leads to 1′-aza-3 : 4-benzpyrene. We have found that the same ring system is readily obtainable from 3-aminopyrene and ethyl acetoacetate.

Ethyl β-3-*Pyrenylaminocrotonate* (I).—To a filtered solution of 3-aminopyrene (3 g.) (Vollmann and co-workers, *ibid.*, p. 109) in ethyl alcohol, ethyl acetoacetate (3·5 c.c.) was added at room temperature. The yellowish-green product was collected after 24 hours and recrystallised from *iso*propyl alcohol; it had m. p. 129°; yield, 85% (Found : C, 79·8; H, 5·5. $C_{22}H_{19}O_2N$ requires C, 80·2; H, 5·8%).

(I.)



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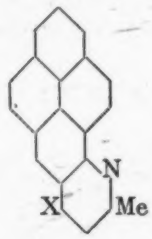

4′-*Hydroxy*-2′-*methyl*-1′-*aza*-3 : 4-*benzpyrene* (II, X = OH).—(I) was diluted with liquid paraffin (5 parts) and heated at 220° for 30 mins. The crystalline product was washed with benzene and recrystallised from nitrobenzene; m. p. 350°; yield, 90% (Found : C, 84·5; H, 5·0; N, 5·2. $C_{20}H_{13}ON$ requires C, 84·8; H, 4·6; N, 5·0%).

4′-*Chloro*-2′-*methyl*-1′-*aza*-3 : 4-*benzpyrene* (II, X = Cl).—The foregoing substance (12·5 g.) was heated with phosphorus pentachloride (10 g.) in ethylene dichloride (20 g.) for 2 hours at 130—140° and for 1 hour at 160—170°. The mixture was poured on ice, and the solid product dissolved in alcohol and reprecipitated with water. It formed yellow crystals, m. p. 207°, from pyridine (Found : Cl, 11·7. $C_{20}H_{12}NCl$ requires Cl, 11·8%).—THE HEBREW UNIVERSITY, JERUSALEM. [*Received, March 6th*, 1942.]

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64. *Chemotherapeutic Studies in the Acridine Series. Part IX. The Chloroaminoacridines.*

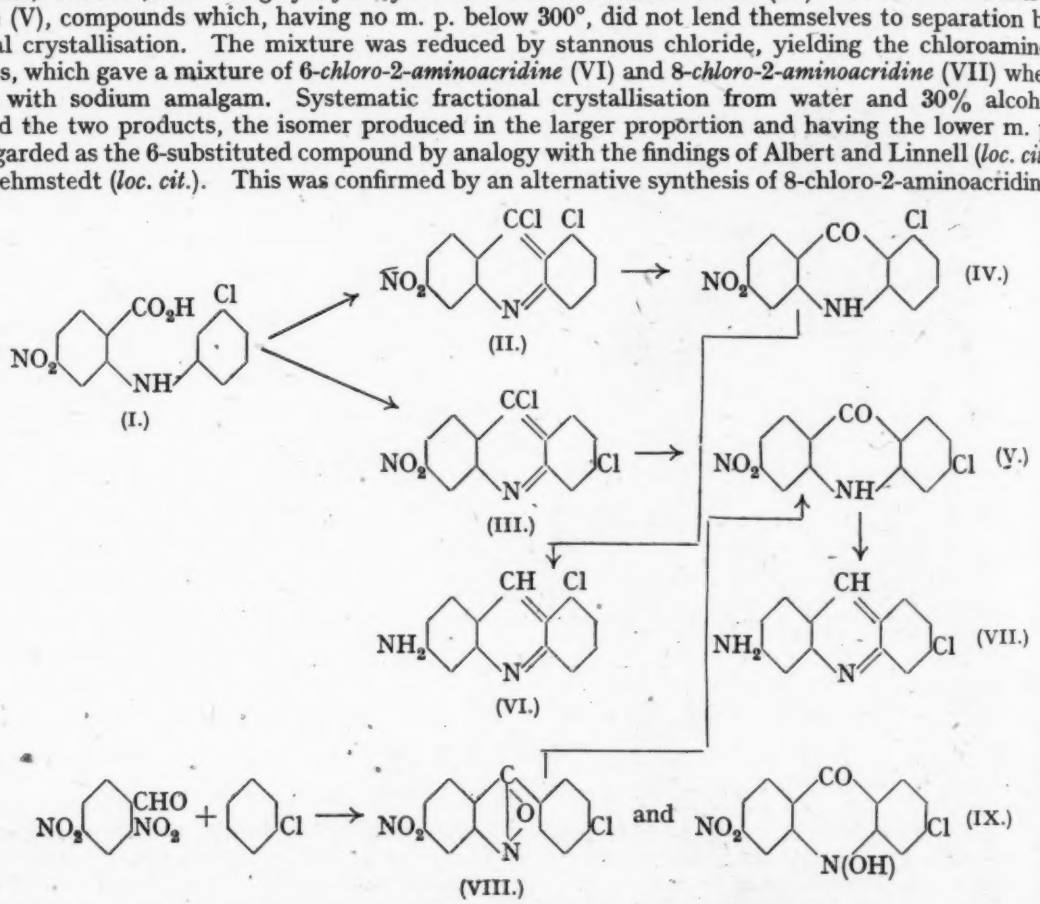
By FRANK R. BRADBURY and WILFRED H. LINNELL.

The preparation of 6- and 8-*chloro*-2-*amino*- and 6- and 8-*chloro*-3-*amino-acridine* is described. The 2- and the 3-amino-compounds were derived from the ring closure of 5- and 4-*nitro*-3′-*chlorodiphenylamine*-2-*carboxylic acid* respectively. In each case the structure of the two isomers was established by an independent synthesis of one of them, and, as in other ring closures of this type, the 6-compound had in each case a lower m. p. and was formed in greater amount than the 8-isomer. 4-*Nitro*-C-(p-*chlorophenyl*)*anthranil* has been isolated from the products of condensation of 2 : 4-dinitrobenzaldehyde and chlorobenzene, and the conversion of this anthranil into 8-chloro-2-nitroacridone by nitrous acid is in agreement with Lehmstedt's mechanism for this condensation.

CHEMOTHERAPEUTIC investigations of the mono- and di-amino-acridines (Albert and Linnell, J., 1936, 88, 1614; 1938, 22; Albert, Rubbo, and Goldacre, *Nature*, 1941, **147**, 332) have shown the simple monoaminoacridines, especially 2-aminoacridine, to be highly active antiseptic substances. On the other hand, many highly active antiseptics have been produced by the introduction of chlorine into the molecule of various phenols (Bechhold and Ehrlich, *Z. physiol. Chem.*, 1906, **47**, 173; Klarmann *et al.*, *J. Amer. Chem. Soc.*, 1929, **51**, 605; 1932, **54**, 3315; 1933, **55**, 2576). The activating effect of chlorine in the phenolic series has been sufficiently pronounced to warrant the study of its effect on the properties of the monoaminoacridines. The preparation of a series of chloroaminoacridines has therefore been undertaken as a further step in the development of antiseptics in the acridine series. This paper describes the preparation of 6-chloro-2-amino-, 8-chloro-2-amino-, 6-chloro-3-amino- and 8-chloro-3-amino-acridine.

The 2-Amino-compounds.—*3'-Chloro-5-nitrodiphenylamine-2-carboxylic acid* (I) was obtained in 38% yield, together with 18% of *p*-nitrobenzoic acid, by refluxing 2-chloro-4-nitrobenzoic acid with *m*-chloroaniline in *n*-butanol in the presence of sodium carbonate and copper during 40 hours. Poorer yields and much tar resulted when the reactants were heated for shorter periods in higher-boiling solvents (amyl alcohol, methyl*cyclo*hexanol).

Ring closure of 3'-substituted diphenylamine-2-carboxylic acids can take place in two ways, giving 6- and 8-substituted acridones. 3'-Chloro-5-nitrodiphenylamine-2-carboxylic acid was treated with excess of phosphorus oxychloride (cf. Lesnianski, *Bull. Acad. Polonaise*, 1929, 81) in the expectation of producing 5 : 6-dichloro-2-nitro- (II) and 5 : 8-dichloro-2-nitro-acridine (III), which should be separable by fractional crystallisation (cf. Albert and Linnell, *loc. cit.*; Lehmstedt, *Ber.*, 1937, **70**, 838). The *meso*-chloro-compounds, however, were largely hydrolysed to 6-chloro-2-nitroacridone (IV) and 8-chloro-2-nitro-acridone (V), compounds which, having no m. p. below 300°, did not lend themselves to separation by fractional crystallisation. The mixture was reduced by stannous chloride, yielding the chloroamino-acridones, which gave a mixture of 6-*chloro*-2-*aminoacridine* (VI) and 8-*chloro*-2-*aminoacridine* (VII) when reduced with sodium amalgam. Systematic fractional crystallisation from water and 30% alcohol separated the two products, the isomer produced in the larger proportion and having the lower m. p. being regarded as the 6-substituted compound by analogy with the findings of Albert and Linnell (*loc. cit.*) and of Lehmstedt (*loc. cit.*). This was confirmed by an alternative synthesis of 8-chloro-2-aminoacridine.



2 : 4-Dinitrobenzaldehyde was condensed with chlorobenzene in the presence of concentrated sulphuric acid, and the product isolated as described by Tanasescu (*Bull. Soc. chim.*, 1927, **41**, 528). The 8-chloro-2-nitroacridone described as the product of this condensation by Tanasescu was obtained in traces only, the main products being 4-*nitro*-C-(p-*chlorophenyl*)*anthranil* (VIII) and 8-*chloro*-2-*nitro*-10-*hydroxy-acridone* (IX). Lehmstedt (*Ber.*, 1932, **65**, 999) has postulated 4-nitro-*C*-(*p*-chlorophenyl)anthranil as an intermediate in the formation of 8-chloro-2-nitroacridone in the Tanasescu condensation, the conversion of anthranil into acridone taking place under the influence of nitrous acid, although he failed to isolate the phenylanthranil. We have converted 4-nitro-*C*-(*p*-chlorophenyl)anthranil into 8-chloro-2-nitro-acridone by treatment with sodium nitrite and sulphuric acid, thus confirming Lehmstedt's mechanism of the condensation. When 2 : 4-dinitrobenzaldehyde was condensed with chlorobenzene in the presence of sodium nitrite and concentrated sulphuric acid, 8-chloro-2-nitroacridone was the main product. Reduction of 8-chloro-2-nitroacridone with stannous chloride gave 8-*chloro*-2-*aminoacridone*, which, when reduced with sodium amalgam in the presence of alcohol and carbon dioxide (cf. Scherlin *et al.*, *J. Gen. Chem. Russia*, 1938, **8**, 880), gave 8-chloro-2-aminoacridine identical with that separated from the 6-chloro-compound by fractional crystallisation.

The 3-*Amino-compounds.*—*3'-Chloro-4-nitrodiphenylamine-2-carboxylic acid* was obtained in 23% yield when potassium 2-chloro-5-nitrobenzoate was condensed with *m*-chloroaniline, in the presence of anhydrous potassium carbonate and copper in refluxing *n*-butanol during 40 hours.

Ring closure of 3'-chloro-4-nitrodiphenylamine-2-carboxylic acid with excess of phosphorus oxychloride gave a mixture of 5 : 6-*dichloro-3-nitroacridine* and 5 : 8-*dichloro-3-nitroacridine.* Although some hydrolysis to the corresponding chloronitroacridones occurred during their isolation, it was possible to free the mixed *meso*-chloro-compounds from acridones by extraction with dry benzene, and subsequent fractional crystallisation from the same solvent separated the two entities. The compound with the lower melting point and formed in greater amount was again regarded as the 6-isomer. 5 : 6-Dichloro-3-nitroacridine was hydrolysed by boiling dilute hydrochloric acid to 6-*chloro-3-nitroacridone*, which gave 6-*chloro-3-aminoacridine* directly when reduced with sodium amalgam. Reduction of the mixed chloronitroacridones with sodium amalgam gave a mixture of 6-chloro-3-aminoacridine and 8-*chloro-3-aminoacridine*, which were separated by fractional crystallisation from dilute alcohol. The identity of the latter compound and hence that of the 6-chloro-3-aminoacridine and the *meso*-chloro-compounds was confirmed by alternative synthesis kindly carried out in the University of Sydney by Dr. Adrien Albert. 2 : 4-Dichlorobenzoic acid was condensed with *p*-phenylenediamine to give 5-chloro-4'-aminodiphenylamine-2-carboxylic acid, which underwent ring closure to give 8-chloro-3-aminoacridine when treated with concentrated sulphuric acid. The product was identical with the specimen isolated by fractional crystallisation.

The four chloroaminoacridines are being submitted to bacteriological tests, the results of which will be published elsewhere.

Experimental.

3'-Chloro-5-nitrodiphenylamine-2-carboxylic Acid (I).—Sodium 2-chloro-4-nitrobenzoate (4·5 g.), anhydrous sodium carbonate (2·0 g.), *m*-chloroaniline (3·3 g.), and precipitated copper (0·1 g.) were heated in refluxing *n*-butanol (20 ml.) for 40 hours. The products of five such experiments were combined, the *n*-butanol and the excess of *m*-chloroaniline removed by steam distillation, and the aqueous residue concentrated, filtered, and cooled; the sodium salt of the product was deposited. A further quantity was obtained by acidifying the mother-liquors and extracting the precipitated acids with boiling water, to remove *p*-nitrobenzoic acid, which was deposited on cooling (3 g.; 18%). The sodium salt, decomposed with dilute hydrochloric acid, gave *3'-chloro-5-nitrodiphenylamine-2-carboxylic acid*, which crystallised from aqueous alcohol (80%) in bright orange needles, m. p. 221—222°. Yield, 38% (Found : N, 9·7; Cl, 12·0. $C_{13}H_9O_4N_2Cl$ requires N, 9·6; Cl, 12·1%).

3'-Chloro-4-nitrodiphenylamine-2-carboxylic Acid.—A mixture of potassium 2-chloro-5-nitrobenzoate (4·8 g.), *m*-chloroaniline (3·3 g.), anhydrous potassium carbonate (2·0 g.), and copper (0·1 g.) was treated as in the preceding preparation. After the removal of *n*-butanol and the excess of *m*-chloroaniline the hot aqueous liquid was filtered. The potassium salt of the product, remaining on the filter free from tar, was crystallised from water (1 in 200) and decomposed with dilute hydrochloric acid, giving *3'-chloro-4-nitrodiphenylamine-2-carboxylic acid*, which crystallised from dilute alcohol in pale yellow needles, m. p. 272—273° (decomp.) (Found : N, 9·8; Cl, 12·4%).

When *cyclo*hexanol replaced the *n*-butanol as solvent, much tar was formed, which, on extraction with boiling water, gave 5-nitrosalicylic acid (0·1 g.), identified by m. p. 227° and the characteristic blood-red colour with ferric chloride solution.

Ring Closures.—3'-Chloro-5-nitrodiphenylamine-2-carboxylic acid (5·0 g.) was refluxed with phosphorus oxychloride (50 g.) until evolution of hydrogen chloride ceased (2 hours); the excess of phosphorus oxychloride was then distilled off, and the residue rubbed with ice-water and aqueous ammonia. A chloroform extract of the lemon-yellow powder (4·8 g.) obtained deposited, on cooling, yellow needles of a mixture of dichloronitroacridines and chloronitroacridones. The whole product was therefore converted into chloronitroacridones by boiling with dilute hydrochloric acid. The mixed chloronitroacridones (2·7 g.), suspended in alcohol (125 ml.), were added gradually to boiling hydrochloric acid (25 ml.) and stannous chloride (10 g.), and the whole refluxed for 3 hours. The solution was filtered, most of the alcohol removed by distillation, and the residue cooled. The mixed tin salts deposited were decomposed with excess of 20% sodium hydroxide solution, and the resulting mixture of chloroaminoacridones washed and dried (1·9 g.). This mixture was finely powdered and suspended in N/2-sodium hydroxide (200 ml.) at 80°, and sodium amalgam (2%; 200 g.) added during 2 hours. Stirring was continued for 2 hours, and the suspension then decanted from the mercury and stirred with free access of air for 2 hours. Filtration gave 1·68 g. of mixed chloroaminoacridines. After one crystallisation from chloroform this mixture was fractionally crystallised from water, and from 30% alcohol. After some twenty crystallisations two fractions of constant m. p. were obtained, 6-*chloro-2-aminoacridine* (VI) (0·13 g.), m. p. 179—180°, and 8-*chloro-2-aminoacridine* (VII) (0·06 g.), m. p. 220—221° (mixed m. p. 212° after softening at 170°). 6-Chloro-2-aminoacridine is readily soluble in alcohol, chloroform and benzene and crystallises from hot water or dilute alcohol in yellow needles. The alcoholic solution is yellow with an intense green fluorescence (Found : N, 12·4; Cl, 15·7. $C_{13}H_9N_2Cl$ requires N, 12·3; Cl, 15·5%). The base and hydrogen chloride in dry ether gave a bright red monohydrochloride, soluble in cold water (1 in 500). 8-Chloro-2-aminoacridine is readily soluble in alcohol, chloroform and benzene, but is less soluble in water and in 30% alcohol than the 6-chloro-compound.

It crystallises in yellow needles from dilute alcohol, the alcoholic solution being yellow with an intense green fluorescence (Found: N, 12·4; Cl, 15·7%). The monohydrochloride is bright red and soluble in about 500 parts of cold water.

3′-Chloro-4-nitrodiphenylamine-2-carboxylic acid (4·0 g.) was refluxed with phosphorus oxychloride (40 g.) for 2 hours, the excess of oxychloride removed, and the residue triturated with ice-water and aqueous ammonia. The product was collected immediately, dried at 100°, and extracted with boiling dry benzene; 2·8 g. of chloronitroacridones remained, which were again treated with phosphorus oxychloride. The combined benzene extracts deposited after concentration 1·8 g. of a yellow powder, which was separated by fractional crystallisation from dry benzene into two fractions of constant m. p., 5 : 6-*dichloro*-3-*nitroacridine* (0·55 g.), m. p. 201°, and 5 : 8-*dichloro*-3-*nitroacridine* (0·15 g.) m. p. 223° (mixed m. p. 198—200°).

5 : 6-Dichloro-3-nitroacridine is soluble in benzene and chloroform, insoluble in water, and slightly soluble in alcohol. It crystallises from dry benzene in pale yellow, feathery needles, which show a strong green fluorescence in filtered ultra-violet light (Found: N, 9·85; Cl, 23·8. $C_{13}H_6O_2N_2Cl_2$ requires N, 9·6; Cl, 24·2%). 5 : 8-Dichloro-3-nitroacridine is readily soluble in chloroform and benzene and slightly soluble in alcohol. It is more readily hydrolysed than the 5 : 6-dichloro-isomer, being converted into 8-chloro-3-nitroacridone by crystallisation from undried benzene or by exposure to the atmosphere for 2 days. Crystallised from sodium-dried benzene, the compound forms feathery yellow needles which show a green fluorescence in ultra-violet light (Found: N, 9·5; Cl, 25·2%).

6-*Chloro*-3-*nitroacridone* was produced when 5 : 6-dichloro-3-nitroacridine was heated with boiling hydrochloric acid (2%; 100 ml.) for 2 hours. The insoluble product was collected, dried at 100°, and crystallised from boiling pyridine. Yield, 95%. The golden plates obtained were slightly soluble in sodium hydroxide solution and readily soluble in alcoholic potassium hydroxide to give a cherry-red solution. The compound was insoluble in aqueous acids, but slightly soluble in glacial acetic acid. It did not melt below 300° (Found: N, 10·2; Cl, 12·9. $C_{13}H_7O_3N_2Cl$ requires N, 10·2; Cl, 12·9%).

6-*Chloro*-3-*aminoacridine*.—6-Chloro-3-nitroacridone (0·5 g.), suspended in N/2-sodium hydroxide (50 ml.) at 80°, was reduced with sodium amalgam (2%; 50 g.) as described above. The product crystallised from alcohol (30%) in yellow needles, m. p. 211—212°, readily soluble in alcohol, chloroform and pyridine, slightly soluble in hot water and in ether. Yield, 66%. The alcoholic solution was yellow with an intense green fluorescence (Found: N, 11·9; Cl, 15·7. $C_{13}H_9N_2Cl$ requires N, 12·3; Cl, 15·5%). The base and excess of hydrogen chloride in ether gave a white dihydrochloride, which was converted into the violet monohydrochloride by washing with ether dried over sodium. The monohydrochloride is soluble in about 400 parts of cold water.

8-*Chloro*-3-*aminoacridine*.—The mixture of 6- and 8-chloro-3-nitroacridones obtained in the ring closure of 3′-chloro-4-nitrodiphenylamine-2-carboxylic acid was reduced with sodium amalgam and sodium hydroxide solution to a mixture of chloroaminoacridines, from which 6-chloro-3-aminoacridine and 8-*chloro*-3-*aminoacridine* were separated by fractional crystallisation from 40% alcohol. The latter is less soluble in dilute alcohol than the 6-chloro-isomer and crystallises from 40% alcohol in brown needles, m. p. 267—269°, readily soluble in alcohol and pyridine and slightly soluble in hot water and in ether; the alcoholic solution shows an intense green fluorescence (Found: N, 12·4; Cl, 15·5%). The red monohydrochloride is soluble in about 400 parts of cold water.

Condensation of 2 : 4-*Dinitrobenzaldehyde with Chlorobenzene*.—2 : 4-Dinitrobenzaldehyde (5 g.), chlorobenzene (20 ml.), and concentrated sulphuric acid (15 ml.) were shaken together during 36 hours. The lower layer was poured into water, and the yellow flocks produced were collected and dried. The upper layer was mixed with benzene and used to extract the dried flocks (three portions each of 300 ml. of boiling solvent). The benzene was removed under reduced pressure, and the semi-crystalline residue crystallised three times from ethyl acetate (very concentrated solutions being used) and once from absolute alcohol. The product (1 g.) was soluble in alcohol, benzene, and ethyl acetate, dissolved in alcoholic potash with a yellow colour, and crystallised in pale yellow needles, m. p. 215°. Fractional crystallisation from alcohol failed to reveal the presence of an isomer, all fractions having m. p. 215°, and the compound was identified as 4-*nitro*-C-(p-*chlorophenyl*)*anthranil* (VIII) by analysis (Found: N, 10·2; Cl, 13·2. $C_{13}H_7O_3N_2Cl$ requires N, 10·2; Cl, 12·9%) and conversion into 8-chloro-2-nitroacridone.

The benzene-insoluble portion of the product of condensation was treated with 5% sodium hydroxide solution and extracted with boiling water until the extracts were no longer red. A *trace* of insoluble material remaining crystallised from aqueous pyridine and showed the red colour with alcoholic potash characteristic of 8-chloro-2-nitroacridone. When the aqueous alkaline extracts were acidified, yellow flocks were deposited, which were further purified by dissolution in hot aqueous alkali (very dilute), filtration, and precipitation by mineral acid, this being repeated three times. Finally the product was crystallised as its sodium derivative from 5% sodium hydroxide solution. Acidification of the pure sodium derivative with dilute hydrochloric acid gave 8-*chloro*-2-*nitro*-10-*hydroxyacridone* (IX) (0·5 g.), m. p. 200°. This compound showed the properties of an *N*-hydroxyacridone (cf. Kliegl, *Ber.*, 1914, **47**, 1629; Lehmstedt, *ibid.*, 1937, **70**, 172): it was insoluble in water and most organic solvents, slightly soluble in boiling toluene, from which it could be recrystallised, soluble in dilute aqueous alkali with the production of a red solution, but precipitable from the solution by sodium chloride or excess of alkali (Found: N, 9·8; Cl, 11·9. $C_{13}H_7O_4N_2Cl$ requires N, 9·6; Cl, 12·2%). When 0·1 g. was dissolved in N-alkali (0·5 ml.) and water (25 ml.) and shaken with methyl sulphate (0·5 g.) for 15 minutes,

yellow flocks of 8-*chloro*-2-*nitro*-10-*methoxyacridone* were formed. These, washed free from alkali, crystallised from acetone–water (4 : 1) in golden plates, decomp. 241°, soluble in acetone, alcohol and benzene, insoluble in aqueous alkali (Found : N, 9·4. $C_{14}H_9O_4N_2Cl$ requires N, 9·2%).

Conversion of 4-*Nitro*-C-(p-*chlorophenyl*)*anthranil into* 8-*Chloro*-2-*nitroacridone*.—The course of this reaction was followed by observing the m. p. (anthranil, 215°; acridone, above 300°) and the colour reaction with alcoholic potash (anthranil, yellow; acridone, red). Under the conditions described by Bamberger (*Ber.*, 1909, **42**, 1707) for the conversion of anthranils into acridones the reaction was incomplete. For complete conversion the anthranil (0·2 g.), concentrated sulphuric acid (4·0 ml.), and sodium nitrite (0·2 g.) were mixed without precaution against rise of temperature, which reached 40° in the initial stages. After ½ hour the mixture was poured into water, and the insoluble material collected and dried. The product, which did not melt below 300° and gave a cherry-red colour with alcoholic potash, was identified as 8-chloro-2-nitroacridone by conversion into 8-chloro-2-nitro-5-(*p*-diethylaminophenyl)acridine by heating with phosphorus oxychloride and diethylaniline as described by Lehmstedt (*loc. cit.*). This compound had the m. p. (236°) and other properties ascribed to it by Lehmstedt.

When 2 : 4-dinitrobenzaldehyde (5·0 g.), chlorobenzene (20 ml.), and sodium nitrite (0·5 g.) were treated with concentrated sulphuric acid (15 ml.), added in small quantities, the temperature being kept below 40°, and the products worked up after 24 hours as described above, 8-chloro-2-nitroacridone (1·4 g.), 4-nitro-*C*-(*p*-chlorophenyl)anthranil (0·3 g.) and 8-chloro-2-nitro-10-hydroxyacridone (0·2 g.) were obtained.

8-*Chloro*-2-*aminoacridone*.—8-Chloro-2-nitroacridone (1·0 g.), stannous chloride (10 g.), concentrated hydrochloric acid (23 ml.), and alcohol (50 ml.) were refluxed together for 1 hour. The yellow crystals of the tin salt of the base deposited on cooling were collected and triturated with excess of 20% sodium hydroxide solution. The base was washed with water and crystallised from dilute alcohol (50%), forming feathery clusters of cream plates. Yield, 70%. 8-*Chloro*-2-*aminoacridone* does not melt below 300°. It is soluble in alcohol, pyridine and glacial acetic acid and slightly soluble in hot water; the alcoholic solution shows a sky-blue fluorescence (Found : N, 11·5; Cl, 14·2. $C_{13}H_9ON_2Cl$ requires N, 11·5; Cl, 14·5%).

8-Chloro-2-aminoacridone (0·4 g.), alcohol (50 ml.), and sodium bicarbonate (10 g.) were maintained at 60—70°, and sodium amalgam (2%; 40 g.) added during 1½ hours, rapid stirring and a steady stream of carbon dioxide being maintained. The sodium bicarbonate and mercury were removed by filtration, the filter washed with alcohol, and the alcoholic solution returned to the flask, heated to 70°, and stirred vigorously for 1 hour whilst a rapid stream of air was passed through the solution. The alcohol was removed under reduced pressure, the residue extracted with boiling 2% hydrochloric acid, and the solution filtered and made alkaline with ammonia. The precipitate, dried and crystallised twice from dilute alcohol, was identical with 8-chloro-2-aminoacridine obtained from 3'-chloro-5-nitrodiphenylamine-2-carboxylic acid (m. p. and mixed m. p. 220—221°).

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65. *The Reaction of 4-Chloroquinaldines and of 2-Chlorolepidines with Ammonia, and the Preparation of the Corresponding Phenyl Ethers.*

By O. G. BACKEBERG and J. L. C. MARAIS.

An investigation of the various methods for preparing 2- and 4-aminoquinoline derivatives from the corresponding chloro-compounds has shown that 4-aminoquinaldines are readily obtained in almost theoretical yield by passing ammonia into a hot phenol solution of the 4-chloro-compounds. When applied to 2-chlorolepidines, this reaction gives the amines only in small yield, the main product being the corresponding phenyl ether; these amines were best prepared by heating the chloro-compound in a sealed tube with the double compound $ZnCl_2,2NH_3$.

4-Chloroquinaldines and 2-chlorolepidines readily formed the corresponding phenyl ethers in almost theoretical yield by heating with phenol for 5 hours at 180°.

4-AMINOQUINALDINES and 2-aminolepidines may be prepared from the corresponding chloro-compounds by the following methods :

(1) By heating in a sealed tube with alcoholic ammonia (Ashley, Browning, Cohen, and Gulbransen, *Proc. Roy. Soc.*, 1933, *B*, **113**, 295), or by the method of Maier-Bode for preparing 3-aminopyridine, in which 3-bromopyridine was heated in a sealed tube with concentrated aqueous ammonia in the presence of copper sulphate as a catalyst (*Ber.*, 1936, **69**, 1534). Although 4-aminoquinaldine is obtained in good yield by these methods, its 6- and 8-methoxy- and -ethoxy-derivatives are not formed from the corresponding chloro-compounds under these conditions. 2-Aminolepidine is obtained only in small yield (Klotz,

Annalen, 1888, **245**, 382), but 6-methoxy- and 6-ethoxy-2-chlorolepidine do not react with ammonia under these conditions.

(2) By reduction of the corresponding phenylhydrazino-compounds. Ephraim (*Ber.*, 1892, **25**, 2706) used this method for preparing 2-aminolepidine; when the method was applied to 6-methoxy- and 6-ethoxy-2-chlorolepidine, the corresponding amines were obtained in 30—40% yield. Backeberg (J., 1938, 1083) obtained 4-aminoquinaldine, as well as its 6- and 8-ethoxy-derivatives, in good yield by this method.

(3) By the method of Diepolder (*J. pr. Chem.*, 1923, **106**, 41), in which the chloro-compound is heated in a sealed tube with the double compound $ZnCl_2,2NH_3$, prepared according to Merz and Müller (*Ber.*, 1886, **19**, 2902). This proved to be the best method for preparing 6-methoxy- and 6-ethoxy-2-aminolepidine from the corresponding chloro-compounds, the yields of these two amines being 70% and 50% respectively.

(4) By passing ammonia into a hot phenol solution of the chloro-compound; this convenient method was used by Jensch (D.R.-P. 591,480) for the preparation of 4 : 6- and 4 : 8-diaminoquinaldine. When dry ammonia was passed into a phenol solution of the chlorolepidines at 180° for 2 hours, the corresponding 2-aminolepidines were obtained in approximately 10% yield; the main product was the corresponding phenyl ether; the chloro-compounds thus react preferentially with the phenol to a large extent. Replacement of the phenol by an inert high-boiling solvent such as *p*-dichlorobenzene yielded no amine at all. If the phenol solution was heated at 180° for 5 hours in the absence of ammonia, the phenyl ether was obtained in almost theoretical yield.

In the case of the 4-chloroquinaldines, the 4-aminoquinaldines were obtained in almost theoretical yield, and the corresponding phenyl ether did not appear to be formed; these amines are thus readily accessible compounds. If, in the absence of ammonia, the phenol solution was heated at 180° for 5 hours, the corresponding phenyl ethers were obtained in almost theoretical yield.

Experimental.

The chloro-compounds employed were: 4-chloroquinoline, 4-chloroquinaldine together with its 6- and 8-methoxy- and -ethoxy-derivatives, 2-chlorolepidine and its 6-methoxy- and 6-ethoxy-derivatives.

Preparation of 4-Aminoquinaldines.—3 G. of the 4-chloroquinaldine (or 4-chloroquinoline) were added to appoximately 10 g. of phenol, and the mixture heated to 180° in an oil-bath. Ammonia, dried over quicklime, was passed through the solution for 2 hours. The hydrochloride of the amine soon began to separate. The excess of phenol was removed by steam-distillation and the clear solution was concentrated to about 70 c.c. by evaporation on the water-bath, cooled, and made alkaline with sodium hydroxide. The amines were obtained in almost theoretical yield in all cases; they were readily obtained pure by crystallisation from water or dilute alcohol.

4-Amino-6-methoxyquinaldine.—Small, pale yellow needles, m. p. 209° (Found: C, 70·4; H, 6·2; N, 14·8. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

4-Amino-8-methoxyquinaldine.—Small colourless needles, m. p. 233° (Found: C, 70·3; H, 6·2; N, 14·8%). These two amines were also prepared by the reduction of the corresponding 4-benzeneazo-compounds (J., 1938, 1083); these azo-compounds were not described in the previous communication.

4-Benzeneazo-6-methoxyquinaldine.—Fine red needles from dilute alcohol, m. p. 73° (Found: N, 15·2. $C_{17}H_{15}ON_3$ requires N, 15·2%).

4-Benzeneazo-8-methoxyquinaldine.—Orange-coloured silky needles from dilute alcohol, m. p. 130° (Found: N, 15·05%).

Preparation of 2-Aminolepidines.—(i) When the procedure described above was carried out with the chlorolepidines, an insoluble oil remained after the excess of phenol had been removed by steam-distillation. The oil readily solidified after cooling and stirring, and was then removed by filtration; this proved to be the phenyl ether (see later). The filtrate, after being concentrated on the water-bath and made alkaline with sodium hydroxide, gave the 2-aminolepidines in approximately 10% yield.

(ii) 2 G. of the chlorolepidine, 10 g. of $ZnCl_2,2NH_3$, and 2 g. of ammonium chloride were heated in a sealed tube at 210—220° for 6 hours. The product was best removed by filling the opened tube with water and keeping it overnight. The required amine, present as the hydrochloride, was extracted from the product by boiling with water, filtration from insoluble zinc salt, and precipitation with sodium hydroxide.

(iii) 2 G. of the chlorolepidine were gently heated over a bare flame with 2·5 g. (2 mols.) of phenylhydrazine. After completion of the reaction, which was accompanied by much frothing, the product was washed with water to remove phenylhydrazine hydrochloride; the crude material, which was sensitive to atmospheric oxidation, was not further purified, and was suitable for reduction to the 2-amino-compound or oxidation to the 2-benzeneazo-compound.

Reduction was effected by refluxing the above product for ½ hour with 10 c.c. of hydriodic acid (*d* 1·67) and 0·5 g. of red phosphorus. The product was diluted with water and filtered, and the filtrate made alkaline with sodium hydroxide and steam-distilled to remove aniline formed during the reduction. The residue from the steam-distillation was extracted with ether, and the amine obtained from the extract as a reddish oil which solidified on rubbing; it was then crystallised from dilute alcohol; yield 30—40%.

For oxidation to the benzeneazo-compound, the above crude phenylhydrazino-compound was dissolved in glacial acetic acid and boiled for a short time with a slight excess of ferric chloride; the benzeneazo-compound was precipitated by pouring the solution into water, and was then crystallised from dilute alcohol; yield, almost quantitative.

2-*Amino*-6-*methoxylepidine*.—Small, pale yellow needles, m. p. 174° (Found: C, 70·35; H, 6·2; N, 14·8. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

2-*Amino*-6-*ethoxylepidine*.—Small colourless needles, m. p. 207° (Found: C, 71·1; H, 6·9; N, 13·9. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 6·9; N, 13·9%).

2-*Benzeneazo*-6-*methoxylepidine*.—Stout, dark red prisms, m. p. 142° (Found: C, 73·55; H, 5·35; N, 15·2. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4; N, 15·2%).

2-*Benzeneazo*-6-*ethoxylepidine*.—Reddish-brown plates, m. p. 162° (Found: C, 74·5; H, 5·8; N, 14·35. $C_{18}H_{17}ON_3$ requires C, 74·2; H, 5·9; N, 14·4%).

Preparation of Phenyl Ethers.—3 G. of the chloro-compound were heated with approximately 10 g. of phenol in an oil-bath at 180° for 5 hours; the excess of phenol was then removed by steam-distillation. In the case of the 4-chloroquinaldines, the residue in the steam-distillation flask was a clear solution of the hydrochloride of the 4-phenoxy-compound, from which the base was obtained in almost theoretical yield by means of sodium hydroxide.

In the case of the 2-chlorolepidines, the 2-phenoxy-compound, obtained in almost theoretical yield, was formed as the free base, and separated as an oil in the steam-distillation flask, after removal of the excess of phenol.

Both classes of ethers crystallised well from dilute alcohol. 4-Phenoxyquinoline was obtained as a thick oil which could not be made to crystallise, although it was precipitated as a solid (which may have been a hydrate) from the aqueous solution of its hydrochloride by sodium hydroxide; when the solid was collected, it changed to a pasty mass which slowly liquefied, and attempts to crystallise it gave only the thick oil referred to. It formed a *picrate*, yellow prisms from alcohol, m. p. 179° (Found: N, 12·55. $C_{15}H_{11}ON,C_6H_3O_7N_3$ requires N, 12·4%), and a *platinichloride*, orange-coloured needles from dilute hydrochloric acid, m. p. 220° (decomp.) (Found: Pt, 22·7. $2C_{15}H_{11}ON,H_2PtCl_6$ requires Pt, 22·9%).

4-*Phenoxyquinaldine* was obtained as the *monohydrate*, colourless silky needles, m. p. 78° (Found: C, 75·6; H, 5·9; N, 5·7; H_2O, 7·2. $C_{16}H_{13}ON,H_2O$ requires C, 75·9; H, 5·9; N, 5·5; H_2O, 7·1%). When dried in a vacuum over phosphoric oxide, it first liquefied and then slowly formed a colourless solid, m. p. 71·5° (Found: C, 81·65; H, 5·55; N, 5·9. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%).

4-*Phenoxy*-6-*methoxyquinaldine*. Small colourless needles, m. p. 112° (Found: C, 77·0; H, 5·6; N, 5·3. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

4-*Phenoxy*-8-*methoxyquinaldine*. Shiny colourless plates, m. p. 147° (Found: C, 76·95; H, 5·5; N, 5·3%).

4-*Phenoxy*-6-*ethoxyquinaldine*. Stout colourless plates, m. p. 121° (Found: C, 77·3; H, 5·9; N, 5·0. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

4-*Phenoxy*-8-*ethoxyquinaldine*. Small, pale yellow needles, m. p. 100° (Found: C, 77·4; H, 6·0; N, 5·1%).

2-*Phenoxylepidine*. Colourless plates, m. p. 48° (Found: C, 81·9; H, 5·6; N, 5·8. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%).

2-*Phenoxy*-6-*methoxylepidine*. Colourless plates, m. p. 70° (Found: C, 77·2; H, 5·5; N, 5·3. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

2-*Phenoxy*-6-*ethoxylepidine*. Stout colourless plates, m. p. 95° (Found: C, 77·4; H, 6·1; N, 5·2. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

The authors thank Prof. Stephen for his interest in the investigation.

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66. *Reactions of Certain Thiazoles and Glyoxalines with Picryl Chloride and 2 : 4-Dinitrochlorobenzene.*

By JOHN MCLEAN and G. D. MUIR.

The object of this investigation was to prepare quaternary thiazolium and glyoxalinium salts containing *N*-picryl or *N*-2 : 4-dinitrophenyl groups.

OWING to difficulties experienced in repeating earlier preparations of simple thiazoles and glyoxalines, it was decided to survey the methods available. New methods of preparing thiazole, 4-methylthiazole and 1 : 4-dimethylthiazole were adopted, and a synthesis of 5-methylthiazole carried out.

The only account found of an attempt to prepare the desired quaternary salts is given by Tomlinson (J., 1936, 1607), who obtained a compound, apparently 2-hydroxy-3-picryl-4-methyl-2 : 3-dihydrothiazole, when 4-methylthiazole and picryl chloride interacted with access to atmospheric moisture. It

was considered that the unstable quaternary salt was first formed, but that the chlorine passed to the 2-position, from which it was rapidly hydrolysed.

Tomlinson's experimental findings have been confirmed and the above compound was also obtained when either picryl chloride or picryl iodide reacted with 4-methylthiazole in cold acetone solution.

The reactions between picryl chloride (and in some cases 2 : 4-dinitrochlorobenzene) and thiazole, 2-methylthiazole, 5-methylthiazole, 2 : 4-dimethylthiazole, 2 : 5-dimethylthiazole, 1 : 4-dimethylglyoxaline and 1 : 5-dimethylglyoxaline, alone and/or in acetone solution, have been studied.

From thiazole and picryl chloride, *thiazole hydrochloride* and a *picrylthiazole* of undetermined orientation were formed, presumably according to the substitutive reaction :

$$2C_3H_3NS + C_6H_2(NO_2)_3Cl = C_3H_2NS{\cdot}C_6H_2(NO_2)_3 + C_3H_3NS,HCl$$

The reaction between 2-methylthiazole and picryl chloride alone or in acetone solution provided the only instance of quaternary salt formation in the thiazoles investigated. The desired *N-picryl-2-methylthiazolium chloride* was obtained, but decomposed in hot alcoholic solution, forming either a picryl-2-methylthiazole or 2-methylthiazole picrate.

In acetone solution, 5-methylthiazole, like thiazole itself, readily yielded the *hydrochloride* of the base and a *picryl-5-methylthiazole* by substitution.

2 : 4-Dimethylthiazole reacted with picryl chloride (and 2 : 4-dinitrochlorobenzene) only at relatively high temperatures and not at all in acetone solution, and the only identifiable product isolated was the *hydrochloride* of the base.

2 : 5-Dimethylthiazole and picryl chloride in acetone solution yielded a highly coloured product which may be an acetone addition compound formed from the picryl-2 : 5-dimethylthiazole at first produced.

The recorded melting points of certain thiazole picrates were found to be incorrect and new values were determined.

N-*Picryl*-1 : 4-*dimethylglyoxalinium chloride*, N-(2 : 4-*dinitrophenyl*)-1 : 4-*dimethylglyoxalinium chloride* and N-(2 : 4-*dinitrophenyl*)-1 : 5-*dimethylglyoxalinium chloride* were readily obtained from the appropriate glyoxalines in acetone solution.

As it would be very difficult to determine experimentally the orientation of the picryl groups in the substituted thiazoles obtained, the authors make the following tentative suggestions :

In view of the conversion of *N*-picryl-2-methylthiazolium chloride into picryl-2-methylthiazole by heat, it seems likely that in the other cases where substitution occurs it is preceded by the formation of unstable quaternary salts as is postulated by Tomlinson in the case of the reaction between 4-methylthiazole and picryl chloride.

Occupation of the C_2-position by a methyl radical appears to disfavour substitution by a picryl group in the cases of 2-methylthiazole and 2 : 4-dimethylthiazole, but when this position is unoccupied, as in thiazole, 4- and 5-methylthiazoles, substitution is rapid. Tomlinson adduces no evidence for ascribing the C_2- and the N_3-position to the hydroxyl and the picryl group respectively rather than the converse, in the product from 4-methylthiazole.

If the postulation that quaternary salt formation precedes picryl substitution is correct, these points favour the view that the C_2-position is the most reactive towards picryl chloride as a substitutive reagent, and lead to the suggestion that the products obtained from thiazole and 5-methylthiazole are 2-*picrylthiazole* and 2-*picryl*-5-*methylthiazole* respectively.

The inactivity of 2 : 4-dimethylthiazole and reactivity of 2 : 5-dimethylthiazole would suggest that of the other two points at which substitution in the ring may occur, the C_4-position is the more probable, it being inferred that when 2 : 5-dimethylthiazole reacts with picryl chloride in acetone solution the product is an acetone derivative of 4-picryl-2 : 5-dimethylthiazole. For a similar reason, it is probable that the product of decomposition of *N*-picryl-2-methylthiazolium chloride is 4-*picryl*-2-*methylthiazole*.

Experimental.

Thiazole.—Popp (*Annalen*, 1889, **250**, 273) prepared thiazole by diazotising aminothiazole with ethyl nitrite in alcohol. The authors were unable to repeat this and attempted alternative methods of preparation.

(1) An attempted preparation from thioformamide and αβ-dichlorodiethyl ether was unsuccessful.

(2) Willstätter and Wirth (*Ber.*, 1909, **42**, 1918) describe the preparation of thiazole from thioformamide and chloroacetaldehyde hydrate; the yield, however, is poor.

(3) It was decided to concentrate on methods employing 2-aminothiazole as starting material, as this is easily obtained from thiourea and αβ-dichlorodiethyl ether. Diazotisation of aminothiazole (23 g.) with nitrous acid, followed by reduction with sodium hypophosphite, gave a poor yield of thiazole (2·5 g.). When reduction was carried out with sodium formate, the yield was even poorer. The method finally adopted was to convert 2-aminothiazole into 2-chlorothiazole, followed by reduction with zinc dust and acetic acid. Schatzmann (*Annalen*, 1891, **261**, 10) prepared 2-chlorothiazole by boiling diazotised 2-aminothiazole with concentrated

hydrochloric acid. Finding this unsatisfactory, the authors adopted the following procedure: 2-Aminothiazole (24 g.) was dissolved in 140 ml. of 5N-hydrochloric acid and cooled to − 5°, and sodium nitrite (16 g.) added in concentrated solution. The cold diazo-solution was added to an ice-cold hydrochloric acid solution of cuprous chloride (prepared from 18 g. of copper carbonate, copper, and hydrochloric acid) and kept overnight. The mixture was then heated to remove a little ether which had been added to prevent frothing, made alkaline, and steam-distilled. The separated 2-chlorothiazole (6 g.) was dried with potassium carbonate; b. p. 138—142°.

A solution of 2-chlorothiazole (13 g.) in glacial acetic acid (50 ml.) was heated almost to boiling, and zinc dust (15 g.) added in small quantities. The solution was refluxed for 2 hours, made alkaline and steam-distilled, all the thiazole coming over with the first 20 ml. of distillate. The thiazole was salted out with potassium carbonate and dried over potassium hydroxide; yield 8·5 g., b. p. 117°. Thiazole picrate, prepared by mixing alcoholic or glacial acetic acid solutions of thiazole and picric acid and recrystallised from alcohol, had m. p. 159—160° (Popp, *Annalen*, 1889, **250**, 275, records m. p. 151°).

Reaction between Thiazole and Picryl Chloride.—Thiazole (0·85 g.) and picryl chloride (2·5 g.) were warmed together for a few moments to aid mixing. The mixture, which set to a hard red mass on cooling, was extracted with boiling acetone (40 ml.). The colourless hygroscopic crystals of *thiazole hydrochloride* which separated on cooling, after being washed with small quantities of acetone, had m. p. 139—140° (Found: Cl, 29·5. C_3H_3NS,HCl requires Cl, 29·2%). The red acetone mother-liquor on concentration yielded further crops of the hydrochloride and then a yellow crystalline solid insoluble in water. Recrystallised from acetone–water (decolourising carbon), this *picrylthiazole* formed bright yellow prisms, m. p. 172° [Found: N, 18·9. $C_3H_2NS{\cdot}C_6H_2(NO_2)_3$ requires N, 18·9%].

The presence of acetone made little difference to the result.

Thiazole and 2 : 4-dinitrochlorobenzene also interacted to form thiazole hydrochloride on heating (confirmed by analysis), but no other product could be isolated.

2-Methylthiazole.—2-Methylthiazole cannot be prepared from thioacetamide and αβ-dichlorodiethyl ether, as the hydrogen chloride liberated decomposes the thioacetamide. Hantzsch's method (*Annalen*, 1889, **250**, 270) was adopted, thioacetamide and chloroacetal being used. 2-Methylthiazole picrate, formed by mixing alcoholic solutions of the base and picric acid, crystallised from hot alcohol in yellow needles, m. p. 153°. Hantzsch records m. p. 145—146°.

Reaction between 2-Methylthiazole and Picryl Chloride.—No reaction took place between 2-methylthiazole and 2 : 4-dinitrochlorobenzene either alone or in acetone solution. A mixture of 2-methylthiazole (1 g.) and picryl chloride (2·5 g.) turned deep purple after a short time and set to a semi-solid crystalline mass; the quaternary salt could not be isolated.

A solution of 2-methylthiazole (5·5 g.) and picryl chloride (13·7 g.) in acetone (40 ml.) became deep purple after 4 days. The *N-picryl-2-methylthiazolium chloride* which separated was collected, washed several times with acetone (yield, 8·2 g.), and recrystallised from boiling alcohol, forming colourless elongated prisms, m. p. 126°, readily soluble in water (Found: Cl, 10·3. $[C_4H_5NS{\cdot}C_6H_2(NO_2)_3]Cl$ requires Cl, 10·3%). From the alcoholic mother-liquor, a small quantity of yellow *picryl-2-methylthiazole*, m. p. 150° (after recrystn. from alcohol), was isolated [Found: N, 18·2. $C_4H_4NS{\cdot}C_6H_2(NO_2)_3$ requires N, 18·1%].

As it was suspected that the picryl substitution product had been formed through decomposition of the quaternary salt by boiling in alcohol, the following experiment was performed: A solution of the quaternary salt (2 g.) in alcohol (40 ml.) was refluxed for 12 hours. On cooling, orange-red clusters separated from the deep red solution. After recrystallisation from alcohol (decolourising carbon), yellow needles, m. p. 153°, were obtained which depressed the m. p. of the picryl-2-methylthiazole, m. p. 150°, described above, but not that of 2-methylthiazole picrate [Found: N, 17·2. Calc. for $C_4H_5NS,C_6H_2(NO_2)_3{\cdot}OH$: N, 17·1%].

4-Methylthiazole.—The preparation of 4-methylthiazole by distilling 2-hydroxy-4-methylthiazole with zinc dust (Arapides, *Annalen*, 1888, **249**, 23) and from 2-amino-4-methylthiazole hydrochloride by diazotisation and reduction being unsatisfactory, it was obtained by reduction of 2-chloro-4-methylthiazole (Tscherniac, J., 1919, **115**, 1072) with zinc and glacial acetic acid (see preparation of thiazole from 2-chlorothiazole above). 4-Methylthiazole was salted out from the steam-distillate with potassium carbonate, dried over potassium hydroxide, and distilled (yield, 12 g. from 23 g. of 2-chloro-4-methylthiazole). The picrate, prepared from the base and picric acid in glacial acetic acid or alcohol and recrystallised from alcohol, had m. p. 182° (Popp, *Annalen*, 1889, **250**, 277, records 174°).

Reaction between 4-Methylthiazole and Picryl Chloride.—No identifiable products were obtained by heating mixtures of 4-methylthiazole and 2 : 4-dinitrochlorobenzene. After confirmation of Tomlinson's finding (*loc. cit.*) that a yellow crystalline compound [m. p. 181° (decomp.)] giving the required analysis for 2-hydroxy-3-picryl-4-methyl-2 : 3-dihydrothiazole (Found: C, 36·7; H, 2·5; N, 16·9; S, 10·0. Calc. for $C_{10}H_8O_7N_4S$: C, 36·6; H, 2·4; N, 17·1; S, 9·8%) was obtained when 4-methylthiazole was warmed with picryl chloride, the experiment was repeated in acetone solution: a solution of 4-methylthiazole (2·0 g.) and picryl chloride (2·5 g.) in acetone (20 ml.) was kept for 3 days at room temperature. The fine yellow needles were separated from the deep red liquor and washed with acetone (yield, 1·7 g.). They melted at 181° (decomp.), alone or mixed with the product obtained by Tomlinson's method. The same compound was also obtained from 4-methylthiazole (1 g.) and picryl iodide (3·4 g.) in acetone (15 ml.) after 3 months. To make certain that the compounds described above were not simply 4-methylthiazole picrate (m. p. 182°, and isomeric with the hydroxypicrylmethyldihydrothiazole), mixed m. p.'s were determined and marked depressions noted in all cases.

5-Methylthiazole.—Bromopropaldehyde hydrate (40 g.) and thiourea (20 g.) were heated together on the water-bath for 1 hour, filtered from a small amount of sulphur, and cooled, and potassium hydroxide solution (50%) added. The potassium salts were removed and on the addition of more potassium hydroxide an oil separated which solidified. The solid was collected and dissolved in ether to remove unchanged thiourea; evaporation of the ether yielded 2-amino-5-methylthiazole (20 g.). This was dissolved in 140 ml. of 5N-hydrochloric acid and diazotised at − 10° with sodium nitrite (16 g.); the diazo-solution was added to an ice-cold solution of cuprous chloride in hydrochloric acid, left overnight, made alkaline, and steam-distilled, yielding 2-chloro-5-methylthiazole (14 g.), b. p. 163—165°. Reduction was carried out as described under thiazole, and 5-methylthiazole (10 g.) obtained, b. p. 141—142°. *5-Methylthiazole picrate*, prepared from the base and picric acid in alcoholic solution, had m. p. 170° [Found : N, 17·2. $C_4H_5NS,C_6H_2(NO_2)_3{\cdot}OH$ requires N, 17·1%].

Reaction between 5-Methylthiazole and Picryl Chloride.—5-Methylthiazole (1 g.) and picryl chloride (1·25 g.) were dissolved in acetone (15 ml.). After 24 hours, a colourless crystalline solid had separated from the red solution. After decantation and washing with acetone, this had m. p. 81° and proved to be *5-methylthiazole hydrochloride* (Found : Cl, 27·6. C_4H_5NS,HCl requires Cl, 26·9%). Dilution of the mother-liquor with water gave a dull yellow solid. Recrystallised from acetone–water (decolourising carbon), this formed bright yellow prisms, m. p. 111°, of a *picryl-5-methylthiazole* [Found : C, 38·5; H, 2·6; N, 17·6. $C_4H_4NS{\cdot}C_6H_2(NO_2)_3$ requires C, 38·7; H, 1·9; N, 18·1%].

2 : 4-*Dimethylthiazole.*—By Hantzsch's method (*Annalen*, 1889, **250**, 265) 25 g. of thioacetamide yielded 15 g. of the thiazole. Prepared by mixing alcoholic solutions of the base and picric acid, and recrystallised from alcohol, 2 : 4-dimethylthiazole picrate was obtained in yellow plates, m. p. 140—141° (Hantzsch records 137—138°).

Reaction between 2 : 4-*Dimethylthiazole and Picryl Chloride.*—Preliminary attempts to obtain a quaternary salt by heating 2 : 4-dimethylthiazole with 2 : 4-dinitrochlorobenzene or picryl chloride at about 180° resulted only in the isolation of the hydrochloride of the base as a sublimate in the reaction flask.

2 : 4-Dimethylthiazole (1·2 g.) and picryl chloride (2·5 g.) were refluxed at 120—130°. After 30 minutes a pale yellow, feathery sublimate formed. This, after resublimation, was colourless, very hygroscopic, and melted at 189°. Analysis proved it to be 2 : 4-*dimethylthiazole hydrochloride* (Found : Cl, 23·6. C_5H_7NS,HCl requires Cl, 23·7%). Further yields of the hydrochloride were obtained by prolonging the heating, but no other product could be isolated from the tarry reaction mixture. Attempts to bring about quaternary salt formation by using acetone and benzyl alcohol as solvents for the reagents were fruitless. There was apparently no reaction in acetone.

2 : 5-*Dimethylthiazole.*—Hubacher's method (*Annalen*, 1890, **259**, 240) gave trifling yields, and Gabriel's method (*Ber.*, 1910, **43**, 1287) was preferred, though the yield was poor.

Prepared by mixing alcoholic solutions of the base and picric acid, and recrystallised from alcohol, 2 : 5-dimethylthiazole picrate was obtained in yellow leaflets, m. p. 172—173° (Hubacher records 166—167°).

Reaction between 2 : 5-*Dimethylthiazole and Picryl Chloride.*—A solution of 2 : 5-dimethylthiazole (1·5 g.) and picryl chloride (3·5 g.) in acetone (20 ml.) became deep purple after 4 hours. After 10 days at room temperature, deep red nacreous plates, m. p. 172° (decomp.) (after washing with hot alcohol), separated. Analysis indicates that this may be an acetone addition *compound* of picryl-2 : 5-dimethylthiazole [Found : S, 8·3; N, 13·6. $C_5H_6NS{\cdot}C_6H_2(NO_2)_3,C_3H_6O$ requires S, 8·4; N, 14·7%].

1 : 4-*Dimethylglyoxaline.*—The base was prepared by the following adaptation of Weidenhagen's method for the preparation of other glyoxalines (*Ber.*, 1935, **68**, 1960) : Copper acetate (60 g.) was dissolved in 20% aqueous ammonia (200 ml.), and formalin (25 ml.) added, followed by methylamine hydrochloride (40 g.) and acetol acetate (20 g.). The mixture was heated at 100° for 15 minutes, cooled, and extracted with chloroform. Separation of a copper salt of a glyoxaline did not take place, hence the N_1-position in the iminazole ring had apparently been methylated. The chloroform extract yielded 1 : 4-dimethylglyoxaline (3·5 g.), b. p. 195—197°, on distillation; this was identified by the formation of the picrate, m. p. 167—168° (Pyman, J., 1910, **97**, 1820).

Reaction between 1 : 4-*Dimethylglyoxaline and Picryl Chloride.*—N-*Picryl*-1 : 4-*dimethylglyoxalinium chloride* separated when solutions of molecular quantities of the reactants were mixed in acetone; it formed pale yellow prisms (after washing with acetone), m. p. 179° [Found : Cl, 10·3. $C_5H_8N_2,C_6H_2(NO_2)_3Cl$ requires Cl, 10·3%].

N-(2 : 4-*Dinitrophenyl*)-1 : 4-*dimethylglyoxalinium chloride*, similarly obtained from 1 : 4-dimethylglyoxaline and 2 : 4-dinitrochlorobenzene, formed orange prisms (after washing with acetone), m. p. 227° [Found : Cl, 12·0. $C_5H_8N_2,C_6H_3(NO_2)_2Cl$ requires Cl, 11·8%].

1 : 5-*Dimethylglyoxaline.*—This base was prepared, along with the 1 : 4-isomer, by Pyman's method (J., 1910, **97**, 1820). The isomers were separated by fractional distillation.

Reaction between 1 : 5-*Dimethylglyoxaline and* 2 : 4-*Dinitrochlorobenzene.*—N-(2 : 4-*Dinitrophenyl*)-1 : 5-*dimethylglyoxalinium chloride* separated when acetone solutions of molecular quantities of the reactants were mixed; it formed yellow prisms (after washing with acetone), m. p. 253° [Found : Cl, 11·5. $C_5H_8N_2,C_6H_3(NO_2)_2Cl$ requires Cl, 11·8%].

The authors wish to record their appreciation of the interest shown in this work by Prof. F. J. Wilson and Dr. I. V. Hopper.

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67. *The Dihydroxystearic Acid of Castor Oil: its Constitution and Structural Relationship to the* 9 : 10-*Dihydroxystearic Acids, m. p.'s* 132° *and* 95°.

By George King.

Oxidation of the naturally occurring dihydroxystearic acid of castor oil, m. p. 141°, with periodic acid has been shown to afford η-aldehydo-octoic acid and nonaldehyde, thus confirming its constitution as a 9 : 10-dihydroxystearic acid.

Hydrogen chloride, or concentrated hydrochloric acid, at 160° converts it into an oily mixture of chlorohydroxystearic acids, which yields an optically active *oxidostearic acid*, m. p. 59·5°, when boiled with dilute aqueous or alcoholic alkali. This on hydrolysis with concentrated alkali affords *r*-dihydroxystearic acid, m. p. 95°. Similarly, *r*-dihydroxystearic acid, m. p. 132°, is converted *via* the chlorohydrins successively into *r*-oxidostearic acid, m. p. 59·5°, and *r*-dihydroxystearic acid, m. p. 95°, and under the same conditions the dihydroxy-acid, m. p. 95°, furnishes *r*-oxidostearic acid, m. p. 55·5°, and finally the dihydroxy-acid, m. p. 132°.

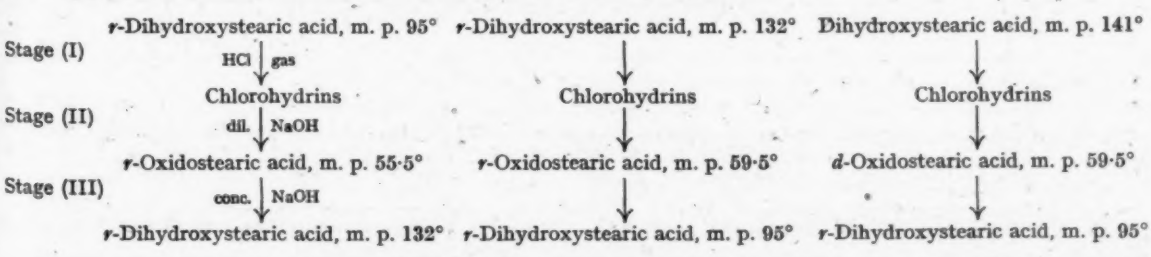
The optical inversion involved in these transformations almost certainly occurs during hydration of the oxide ring, and the conclusion is drawn that the dihydroxy-acid from castor oil is an active component of *r*-dihydroxystearic acid, m. p. 132°. It is, however, virtually internally compensated, its activity being too feeble for accurate measurement.

Configurational formulæ have been provisionally assigned to these acids.

It has long been known that a dihydroxystearic acid, m. p. 141°, occurs amongst the products of hydrolysis of castor oil. As a deposit from crude ricinoleic acid obtained from the oil, it was mentioned by Juillard (*Bull. Soc. chim.*, 1895, **13**, 246) and subsequently by Meyer (*Arch. Pharm.*, 1897, **235**, 185), Mühle (*Ber.*, 1913, **46**, 2095), and Fahrion (*Chem. Zentr.*, 1916, II, 580), but its constitution remained uncertain. More recently, Toyama and Ishikawa (*Bull. Soc. Chem. Japan*, 1936, **11**, 735) showed that the hydroxyl groups occupy the 9 : 10-positions by chromic acid oxidation to nonoic and azelaic acids, and by conversion of the methyl ester, m. p. 111°, into a mixture of oleic and elaidic acids *via* methyl dibromostearate. Polarimetric examination by these authors of the free acid and of its methyl ester revealed too feeble an optical activity to be measured with certainty, but it was considered that both were slightly dextrorotatory in methyl-alcoholic solution. In any case, the acid must be a component of one or other of the two racemic dihydroxystearic acids, m. p.'s 95° and 132°, or, much less probably, a mixture of diastereoisomerides.

Resolution of the racemic acids through their strychnine salts was claimed by Freundler (*Bull. Soc. chim.*, 1895, **13**, 1053) and by Inoue and Suzuki (*Proc. Imp. Acad. Tokyo*, 1931, **7**, 261), but unfortunately the melting points of the optically active isomerides were not recorded. According to Freundler, the rotatory power of the optically active acids was so small as to render an absolute differentiation almost impossible, whereas the latter workers recorded $[\alpha]_D$ + 23·2° and − 23·6° for the *d*- and the *l*-isomeride of the dihydroxy-acid, m. p. 132°; $[\alpha]_D$ + 27·6° and − 27·45° for those of the acid, m. p. 95°. Toyama and Ishikawa (*loc. cit.*), on the other hand, were unable to resolve the racemic acids by means of the strychnine salts.

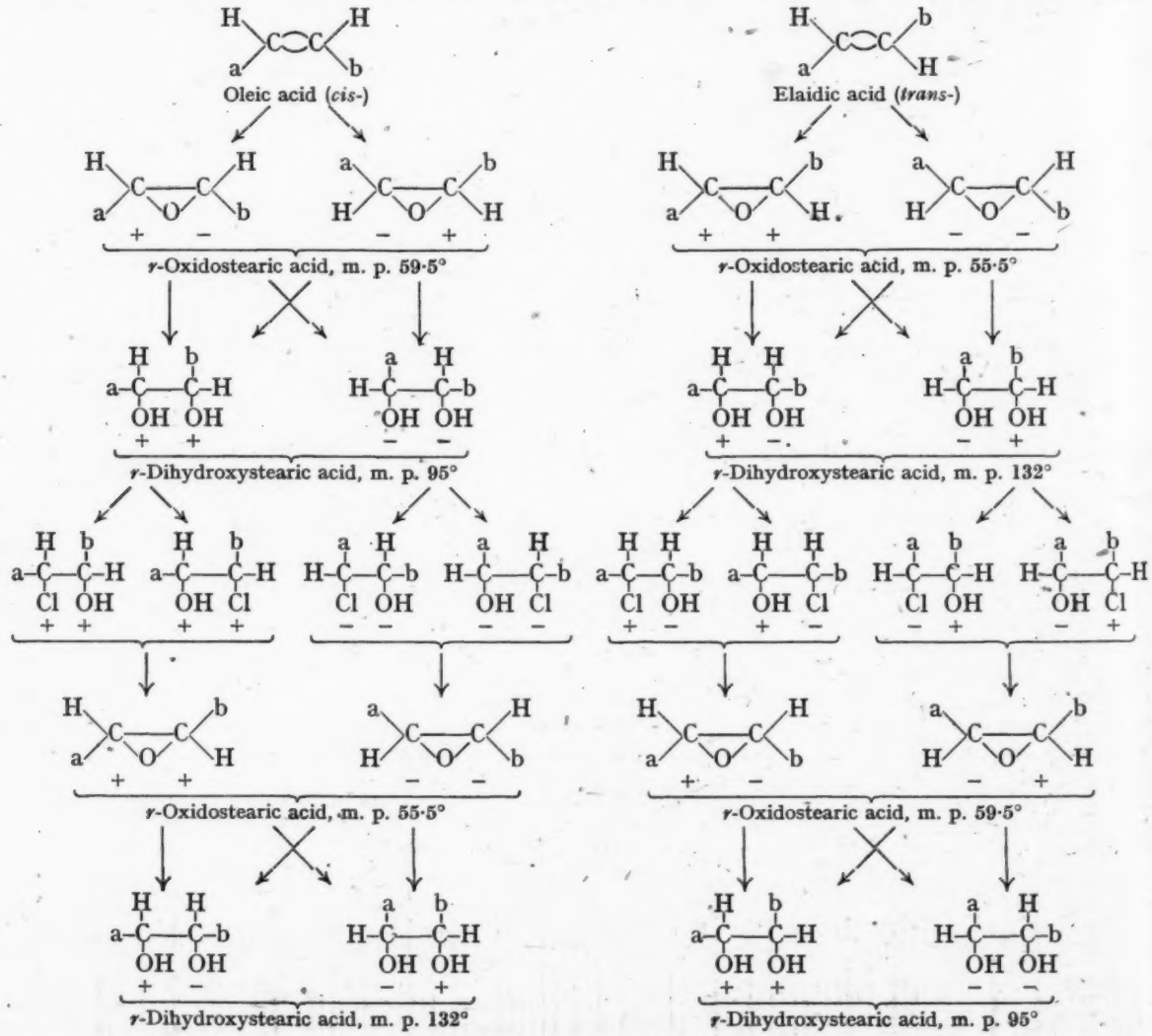
The purpose of the present investigation was to establish the constitution of the dihydroxystearic acid from castor oil, and to determine its relationship to the racemic acids. As a result, unequivocal evidence has now been obtained that the hydroxyl groups occupy the 9 : 10-positions, since oxidation with periodic acid has been shown to afford nonaldehyde and η-aldehydo-octoic acid (cf. King, J., 1938, 1826), and it is reasonably certain that the acid is an active component of the racemic acid, m. p. 132°. Although attempts to resolve the racemic acids through their strychnine salts were unsuccessful, evidence of the stereochemical relationships of all three acids was obtained by their interconversion through the corresponding chlorohydroxy- and oxido-stearic acids, as summarised below:



From stereochemical considerations, it is clear that complete inversion of one of the two asymmetric groups occurring at either stage (I) or stage (III) of the transformation, *i.e.*, during the replacement of hydroxyl by chlorine, or on fission of the oxide ring, would satisfactorily account for the mutual conversion

of the two racemic dihydroxy-acids. According to Böeseken and Belinfante (*Rec. Trav. chim.*, 1926, **45**, 917), inversion occurs during the hydration of the oxide ring in an acid medium, and Esafov (*J. Gen. Chem. Russ.*, 1937, **7**, 1403) suggested that isomerisation always takes place when α-oxides are hydrated. Esafov found that iodohydroxystearic acid from oleic acid gives dihydroxystearic acid, m. p. 132°, on treatment with dilute alkali, presumably by direct substitution of hydroxyl for halogen, whereas with concentrated alkali an oxidostearic acid is formed as an intermediate product, affording on hydrolysis the dihydroxy-acid, m. p. 95°. In the absence of any certain knowledge concerning the relative configurations of the iodohydroxy- and dihydroxy-stearic acids, however, similar results might be anticipated if a Walden inversion occurred instead during the replacement of halogen by hydroxyl.

Each of the two *r*-dihydroxystearic acids may give two pairs of antimeric chlorohydroxystearic acids with hydrogen chloride under controlled conditions. These in turn, by removal of hydrogen chloride in the presence of alkali, will afford one pair of enantiomorphously related oxidostearic acids, but the identity of the externally compensated oxido-acid so formed will depend on whether or not inversion has occurred during stage (I). The scheme below has been drawn up on the assumption that inversion occurs only during fission of the oxide ring [stage (III)]. Under these conditions any one of the four optically active dihydroxy-acids may furnish an active oxido-acid, whereas if inversion occurred during replacement of –OH by –Cl [stage (I)], the resulting oxido-acid would be externally compensated. The further assump-


Oleic acid (*cis*-)
Elaidic acid (*trans*-)
r-Oxidostearic acid, m. p. 59·5°
r-Oxidostearic acid, m. p. 55·5°
r-Dihydroxystearic acid, m. p. 95°
r-Dihydroxystearic acid, m. p. 132°
r-Oxidostearic acid, m. p. 55·5°
r-Oxidostearic acid, m. p. 59·5°
r-Dihydroxystearic acid, m. p. 132°
r-Dihydroxystearic acid, m. p. 95°

(a = $CH_3 \cdot [CH_2]_7 -$; b = $-[CH_2]_7 \cdot CO_2H$.)

tion has been made that the rotations contributed by the two asymmetric groups in *r*-oxidostearic acid, m. p. 55·5° [formed also by autoxidation of elaidic acid (Ellis, *Biochem. J.*, 1936, **30**, 756)], are of the same

sign, which finds a parallel in the oxidation of fumaric to racemic acid, and is in harmony with the extraordinarily feeble rotation exhibited by the dihydroxy-acid, m. p. 141°, in which it is reasonable to suppose the two asymmetric groups have opposing influences. The dihydroxy-acid from castor oil does, in fact, yield an optically active (d-)*oxidostearic acid*, m. p. 59·5° (*via* the chlorohydrins), which, although not identical with *r*-oxidostearic acid, m. p. 59·5°, gives the same dihydroxy-acid, m. p. 95°, on hydrolysis. The conclusion may be drawn that the active oxido-acid is a component of *r*-oxidostearic acid, m. p. 59·5°, and that the dihydroxy-acid from castor oil is itself an active component of the acid, m. p. 132°. These results lend strong support to the view that isomerisation occurs on hydration of the oxide ring. Further, it is clear that the dihydroxy-acid from castor oil cannot be a mixture of diastereo-isomerides such as *d*A*d*B + *d*A*l*B, where A and B represent the two asymmetric groups in the molecule, since this would lead to the production of a *mixture* of (diastereo-)isomeric oxido-acids, which in turn would furnish a *mixture* of the two racemic dihydroxy-acids, contrary to the observed facts.

Dihydroxystearic acid, m. p. 141°, was found by the author to be virtually internally compensated, its extremely feeble optical activity, combined with its low solubility in the usual solvents, making an accurate determination of its rotatory power practically impossible, although the polarimeter used was capable of detecting an angular rotation of 1′ or more [the instrument used by Toyama and Ishikawa (*loc. cit.*) could not detect with certainty a rotation of less than 15′].

Oleic and elaidic acids have been included in the scheme not only for the sake of completeness, but also because they contribute materially to a full appreciation of the stereochemical relationships existing between the oxidised acids. It may be relevant to point out that the oxidation of oleic and elaidic acids by alkaline permanganate to the dihydroxystearic acids, m. p.'s 132° and 95° respectively, appears to involve normal *cis*-addition of two hydroxyl groups, if the proposed configurational formulæ are correct (cf. Hilditch, J., 1926, 1828; Hilditch and Lea, J., 1928, 1576). At the same time a rational explanation is offered of the formation of the dihydroxy-acid, m. p. 95°, from oleic acid with the aid of perbenzoic acid (Pigulevski and Petrova, *J. Russ. Phys. Chem. Soc.*, 1926, **58**, 1062; Böeseken and Belinfante, *loc. cit.*; Nicolet and Poulter, *J. Amer. Chem. Soc.*, 1930, **52**, 1189), where an intermediate oxido-compound is known to be formed. It is still uncertain, however, whether a similar explanation may be applied to the use of Caro's acid (Albitski, *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 810), and of hydrogen peroxide in neutral or acid solution (Hilditch, *loc. cit.*), since in these cases, so far as is known, no intermediate oxidostearic acid has as yet been isolated (see, *e.g.*, Hilditch and Lea, *loc. cit.*). However this may be, the configurations here assigned must be regarded as tentative only, and further evidence in this connexion is being sought.

The mutual transformation of the two *r*-dihydroxystearic acids was accomplished by Albitski (*loc. cit.*, p. 788) through the intermediate formation of bromoacetoxy- or diacetoxy-stearic acid, but from the latter mixtures usually resulted, and in the present investigation isomerism appears to have been complete.

The melting points obtained for the *r*-oxidostearic acids fully confirm those recorded by Ellis (*loc. cit.*) (cf. Pigulevski and Petrova, *loc. cit.*; Böeseken and Belinfante, *loc. cit.*; Nicolet and Poulter, *loc. cit.*; Hashi, *J. Soc. Chem. Ind. Japan*, 1936, **39**, 162B).

Experimental.

Isolation and Physical Properties of 9 : 10-*Dihydroxystearic Acid, m. p.* 141°.—The source of the acid was the sludge deposited on long standing from technical ricinoleic acid. This was filtered with suction, and the finely crystalline residue washed with light petroleum. After several crystallisations from alcohol, the acid separated in small, colourless, hexagonal plates, m. p. 141° (Found: C, 68·3; H, 11·2; equiv., 316. Calc. for $C_{18}H_{36}O_4$: C, 68·3; H, 11·4%; equiv. 316). In solubility, the product closely resembled the synthetic 9 : 10-dihydroxystearic acid, m. p. 132°, being very sparingly soluble in light petroleum, cold chloroform and benzene, and only slightly soluble in cold alcohol and ether. The saturated solution in alcohol at 20° contained 0·82 g. per 100 ml., and the solubility of the acid, m. p. 132°, was 0·68 g., and that of a mixture of the acids, 0·89 g. per 100 ml. of solution at the same temperature. It was inferred that the acid, m. p. 132°, was a true racemic compound rather than a *dl*-conglomerate, assuming the acid from castor oil to be one of its optically active components.

Polarisation of a warm alcoholic solution of the acid, m. p. 141°, gave as a result of numerous readings $[\alpha]_D^{50°} - 0·15°$ ($l = 2$, $c = 3·8$), but the rotation observed (0·7′) was probably within the limits of experimental error. The addition of 5% of boric acid to the solution had no measurable effect on the rotation.

Oxidation with Periodic Acid.—Dihydroxystearic acid, m. p. 141°, (6 g.) in alcohol (300 ml.) was oxidised at 40° with periodic acid as previously described for the acid, m. p. 132° (King, *loc. cit.*, p. 1827), yielding nonaldehyde (2·74 g.), b. p. 185—190° (Found: C, 75·7; H, 12·9. Calc. for $C_9H_{18}O$: C, 76·0; H, 12·8%) [2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic specimen 106·5° (Found: C, 56·0; H, 7·2; N, 16·9. Calc. for $C_{15}H_{22}O_4N_4$: C, 55·9; H, 6·9; N, 17·4%); semicarbazone, slender rhombic and hexagonal plates from dilute alcohol, m. p. and mixed m. p. with an authentic specimen 101·5°], and η-aldehydo-octoic acid (2·1 g.), m. p. 38° (Found: equiv., 173. Calc. for $C_9H_{16}O_3$: equiv., 172) [semicarbazone, m. p. 166·5°

(Found: C, 52·3; H, 8·6; N, 18·0; equiv., 229. Calc. for $C_{10}H_{19}O_3N_3$: C, 52·4; H, 8·3; N, 18·3%; equiv., 229); 2 : 4-dinitrophenylhydrazone, orange prisms or blades from methyl alcohol, m. p. and mixed m. p. with an authentic specimen 122·5°].

Special care had to be taken in the extraction of these products to use ether free from peroxides, as otherwise the semialdehyde was more or less oxidised to bis-α-hydroxy-ω-carboxyoctyl peroxide, m. p. 112·5° (this vol., p. 219).

Conversion of Dihydroxystearic Acid, m. p. 141°, *into* d-9 : 10-*Oxidostearic Acid, m. p.* 59·5°, *and Dihydroxystearic Acid, m. p.* 95°.—Attempts to racemise the acid from castor oil by heating with water or 0·4N-sulphuric acid in a sealed tube at 160° for 1 hour, by boiling with N/2-alcoholic potassium hydroxide, or by heating with N/4-aqueous sodium hydroxide in a sealed tube at 165° for 8 hours were ineffectual, the acid in each case being recovered substantially unchanged (Inoue and Suzuki, *loc. cit.*, reported that the optical isomerides of the dihydroxy-acids, m. p.'s 132° and 95°, were readily racemised during the formation of their potassium salts, or on boiling in alcohol for 30 minutes).

Dry hydrogen chloride was passed at a moderate rate through the dihydroxy-acid (2·85 g.), heated in an open tube in a glycerol bath at 160° for 4 hours. The viscous oily product, consisting of a mixture of chlorohydroxystearic acids, was washed by decantation, and boiled (without further purification) with 2N-sodium hydroxide (75 ml.) for 7 hours (or with 2N-alcoholic potassium hydroxide for 2 hours). The solid product obtained on acidification was collected, dried, and extracted with warm light petroleum (30—40 ml.). A small insoluble fraction was removed by filtration, and crystallised successively from benzene and methyl alcohol, separating from the latter in rectangular plates (0·26 g.), m. p. 94°, not depressed by admixture with authentic dihydroxystearic acid, m. p. 95°, prepared by oxidising elaidic acid with permanganate in alkaline solution (Found: C, 68·0; H, 11·1%; equiv., 317).

When the light petroleum filtrate was concentrated and cooled in ice, a deposit of d-*oxidostearic acid* (1·6 g.) was obtained. This crystallised from methyl alcohol and acetone in truncated triangular plates, m. p. 59·5°, usually separating in six- or eight-sided forms, $[\alpha]_D^{19°}$ in alcohol + 0·29° ($l = 2$, $c = 8·54$) (Found: C, 72·3; H, 11·2; equiv., 298. $C_{18}H_{34}O_3$ requires C, 72·4; H, 11·5%; equiv., 298), readily soluble in most organic solvents other than light petroleum.

Hydrolysis of the oxidostearic acid (0·52 g.) was best effected by heating with 7N-potassium hydroxide (6 ml.) in a sealed tube at 170° for 5 hours. The product was dissolved in sufficient hot water, filtered from silica, and acidified with hydrochloric acid. After cooling, the precipitated acid was collected, and crystallised successively from benzene (*ca.* 30 ml.) and methyl alcohol, separating from the latter in rectangular plates (0·34 g.), m. p. 94·5°, not depressed by admixture with authentic dihydroxystearic acid, m. p. 95°.

As an alternative to hydrogen chloride, concentrated hydrochloric acid was sometimes used for the preparation of chlorohydroxystearic acids. For this purpose the dihydroxy-acid (2 g.), m. p. 141°, was heated with concentrated hydrochloric acid (5 ml.) in a sealed tube at 160° for 4 hours. Subsequent hydrolysis of the chlorohydrins afforded a yield of oxidostearic acid comparable with that obtained with the aid of hydrogen chloride, but the product was usually associated with varying amounts of an impurity, from which the more soluble oxido-acid was separated by fractional crystallisation from 80% alcohol. This substance furnished rhombic plates, m. p. 73·5°, and was possibly a mixture of 9- and 10-ketostearic acids, although its identity was not definitely established [Found: C, 72·4; H, 11·3; equiv., 301; *M* (Rast), 328. Calc. for $C_{18}H_{34}O_3$: C, 72·4; H, 11·5%; equiv., 298]. It was readily soluble in ether, benzene, and warm light petroleum, but sparingly soluble in the last at 20°, and differed sharply from oxidostearic acid in being resistant to hydrolysis and unaffected by periodic acid (the oxido-acids appeared to be oxidised by periodic acid in much the same way as the dihydroxy-acids, the characteristic odour of nonaldehyde being at once apparent).

Conversion of Dihydroxystearic Acid, m. p. 132°, *into* r-*Oxidostearic Acid, m. p.* 59·5°, *and Dihydroxystearic Acid, m. p.* 95°.—Dihydroxystearic acid (3·9 g.), m. p. 132°, was treated with hydrogen chloride at 160°, and the product boiled with 2N-alkali in the manner described above. Fractionation from light petroleum then afforded dihydroxystearic acid (0·9 g.), m. p. and mixed m. p. with an authentic specimen 94°, and *r*-oxidostearic acid (1·97 g.), crystallising from acetone in long slender laminæ, m. p. 59·5°, not depressed by admixture with a specimen of oxidostearic acid of the same m. p. kindly supplied by Dr. G. W. Ellis, and prepared from oleic acid by treatment with hypochlorous acid, followed by alcoholic sodium ethoxide (Ellis, *loc. cit.*, p. 757) (Found: C, 72·5; H, 11·5%; equiv., 298). When mixed with an equal quantity of *d*-oxidostearic acid of the preceding experiment (which is one of its active components, and, although having the same m. p., differs markedly from it in crystalline form), the m. p. was depressed by a small but definite amount to 56°.

Hydrolysis of the racemic oxidostearic acid furnished a good yield of dihydroxystearic acid, m. p. and mixed m. p. with an authentic specimen, 94·5°, separating from methyl alcohol in characteristic rectangular plates. No trace of the dihydroxy-acid, m. p. 132°, as a result of hydrolysis was found either in this or in the preceding experiment.

Conversion of Dihydroxystearic Acid, m. p. 95°, *into* r-*Oxidostearic Acid, m. p.* 55·5°, *and Dihydroxystearic Acid, m. p.* 132°.—By the procedure described above, dihydroxystearic acid (1·20 g.), m. p. 95°, gave dihydroxystearic acid (0·05 g.), m. p. and mixed m. p. with an authentic specimen prepared by oxidising oleic acid with alkaline permanganate 131·5°, separating from alcohol in rhombic and hexagonal plates, and *r*-oxidostearic acid (0·77 g.), which crystallised from methyl alcohol in small rhombic plates, m. p. 55·5° (Found: C, 72·5; H, 11·6%; equiv., 299). The m. p. of the latter was not depressed by admixture with a specimen of oxidostearic acid, m. p.

55·5°, kindly supplied by Dr. G. W. Ellis and prepared by autoxidation of elaidic acid. Mixed with *r*-oxidostearic acid, m. p. 59·5°, or *d*-oxidostearic acid, m. p. 59·5°, the m. p. was depressed to 48—49°.

Hydrolysis of this oxido-acid afforded a good yield of dihydroxystearic acid, m. p. and mixed m. p. with an authentic specimen 132° (Found: equiv., 315). No trace of the dihydroxy-acid, m. p. 95°, was found as a result of hydrolysis.

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68. *Studies in the Sterol Group. Part XLIV. The Oxidation of Phytosterols with the Oppenauer Reagent.*

By E. R. H. Jones, P. A. Wilkinson, and (in part) R. H. Kerlogue.

A comparative study of the behaviour of cholesterol and of the phytosterols, fucosterol, stigmasterol and β-sitosterol on oxidation by the Oppenauer method has been made. The αβ-unsaturated ketones, cholestenone, *fucostadienone* and stigmastadienone are all isolated in good yield, but β-sitosterol, with constants in agreement with those recorded in the literature, yields a mixture of ketones from which sitostenone, m. p. 83—84°, can be separated by chromatographic fractionation, in only 15% yield. The absorption spectra of the ketones and of their oximes, semicarbazones and 2 : 4-dinitrophenylhydrazones have been determined and the expected uniformity both in location and intensity of the maxima has been observed.

In a recent publication (Heilbron, Jones, Roberts, and Wilkinson, J., 1941, 344) the isolation of β-sitosterol from crepe rubber was described. On oxidation by the Oppenauer method (*Rec. Trav. chim.*, 1937, **56**, 137) this sterol gave in poor yield an αβ-unsaturated ketone, m. p. 92—93° (max. 2410 A., $\log \varepsilon = 4{\cdot}23$). This melting point is somewhat higher than that given in the literature for sitostenone from β-sitosterol and this fact, together with the knowledge that a similar oxidation of cholesterol yields Δ^4-cholestenone in excellent yield, made it desirable to study comparatively the oxidation of cholesterol and of the phytosterols, fucosterol, stigmasterol and β-sitosterol.

The αβ-unsaturated ketone, *fucostadienone*, m. p. 94°, was obtained in 50% yield from fucosterol by the Oppenauer method and similarly, stigmasterol yielded stigmastadienone, m. p. 125°, in 58% yield. The latter ketone (designated stigmastenone) was prepared previously by Marker and Wittle (*J. Amer. Chem. Soc.*, 1937, **59**, 2704) by dehydrogenation of stigmasterol with copper powder and by Marker and Rohrmann (*ibid.*, 1938, **60**, 1073) by dehydration of 4-hydroxystigmasterol, the melting point of the ketone being recorded as 94° in each case. The use of a modified Oppenauer method (acetone and aluminium *iso*propoxide; Schering-Kahlbaum A.-G., F.P. 822,551; *Chem. Zentr.*, 1938, II, 120) gave a stigmastadienone of m. p. 105°, but Fernholz and Stavely (*J. Amer. Chem. Soc.*, 1939, **61**, 2956), employing *cyclo*hexanone as the hydrogen acceptor, obtained a product (and semicarbazone) identical with that obtained by us. The same compound was also obtained by Fernholz and Stavely (*loc. cit.*) by Oppenauer oxidation and subsequent debromination of stigmasterol 22 : 23-dibromide (after purification through the semicarbazone).

The wheat-germ sitosterol employed in this investigation furnished a crude β-sitosteryl acetate which, after sixteen crystallisations from ethyl acetate, had m. p. 125°, $[\alpha]_D^{20°} - 35°$. On hydrolysis this yielded β-sitosterol, m. p. 136—137°, $[\alpha]_D^{20°} - 32°$, the constants of both sterol and acetate thus approximating closely to those usually quoted for pure β-sitosterol (for summary see Heilbron and Jones, *Ann. Rev. Biochem.*, 1940, **9**, 163). Oxidation of this β-sitosterol with the Oppenauer reagent gave a product, the heterogeneity of which was revealed by chromatographic analysis on alumina from light petroleum solution. By this method we have succeeded in isolating from the mixture, only however in 15% yield, sitostenone, m. p. 83—84°, comparing favourably in melting point and in melting point of the semicarbazone with specimens obtained by previous workers employing other methods (Marker and Wittle, *loc. cit.*; Marker, Kamm, and Wittle, *J. Amer. Chem. Soc.*, 1938, **60**, 1072; Heiduschka and Gloth, *Arch. Pharm.*, 1915, **253**, 415; Coffey, Heilbron, and Spring, J., 1936, 738). It should be noted that the intensity of light absorption at the maximum (2410 A.) is more than twice as high as that reported by the latter authors for a specimen of sitostenone melting only 3° lower. We have observed this phenomenon in other cases, particularly with materials purified by chromatographic fractionation.

Accompanying this sitostenone was some unoxidised sterol (10%), together with a similar quantity of a second ketonic substance, m. p. 143—145°, $[\alpha]_D^{20°} + 52°$. Its absorption spectrum (see Experimental) indicates that this material is probably a mixture in which a saturated ketone predominates along with

some 10% of an αβ-unsaturated ketone. The fact that this material is dextrorotatory, together with its facile elution from alumina and the light absorption of its 2 : 4-dinitrophenylhydrazone, supports the above contention, although not wholly eliminating the possibility of the presence of an ethenoid linkage in the ketone in a non-conjugated position. It is possible that this material is impure sitostanone either present as an impurity in the β-sitosterol, or having been produced from sitostanol present as a contaminant. Such oxidations of saturated sterols under these conditions have not been reported previously, but we have observed (with B. Heath-Brown) that under more vigorous conditions (aluminium *iso*propoxide and *cyclo*hexanone) the Oppenauer method can effect partial conversion of cholestanol into cholestanone. In a recent publication Reich and Reichstein (*Arch. Intern. Pharmacodynamie Thérapie*, 1941, **65**, 415) report the oxidation of the 3-hydroxyl group of saturated steroids by a modification of the Oppenauer method employing aluminium phenoxide. The chromatographic analysis of the crude oxidation product has revealed yet another αβ-unsaturated ketone (max. at 2410 A., $E^{1\%}_{1cm.} = 380$), the further investigation of which will be reported in a subsequent communication.

The results described above raise the question as to whether β-sitosterol as described in the literature is indeed a homogeneous substance and the wider issue as to whether crystallisation alone can be relied upon for the resolution of phytosterol mixtures. We believe that oxidation by the Oppenauer method, followed by chromatographic resolution of the product, provides a reliable method of determining the homogeneity or otherwise of a phytosterol and this is being tested by further experimental work.

The four main unsaturated ketones described above have been characterised by the preparation of oximes, semicarbazones and 2 : 4-dinitrophenylhydrazones, the light absorption data for these substances being indicated in the accompanying table.

	Oxime.		Semicarbazone.		2 : 4-Dinitrophenylhydrazone.	
	A.	ε.	A.	ε.	A.	ε.
Cholestenone	2405	18,000				
	3120	100	2400	23,000	2705	26,000	3910	32,000
Fucostadienone	2400	17,000				
	3100	70	2405	23,000	2715	27,000	3920	32,000
Stigmastadienone	2410	17,000				
	3075	75	2400	22,000	2710	29,000	3920	30,000
Sitostenone	2410	17,000				
	3070	75	2400	20,000	2720	25,000	3920	32,000

(The absorption spectra of the ketones and oximes were determined in alcoholic solution, those of the semicarbazones and dinitrophenylhydrazones in chloroform.)

The absorption spectra of cholestenone, its oxime and semicarbazone have been recorded by other workers (Heilbron and Morton, J., 1928, 48; Menschick, Page, and Bossert, *Annalen*, 1932, **495**, 225; Mohler, *Helv. Chim. Acta*, 1937, **20**, 289) and the significance of the location of the main band in the spectrum of cholestenone and other αβ-unsaturated ketones has been discussed by Woodward (*J. Amer. Chem. Soc.*, 1941, **63**, 1123) and by Evans and Gillam (J., 1941, 815). The position of the principal band in the absorption spectra of 2 : 4-dinitrophenylhydrazones of saturated aldehydes and ketones lies between 3500 and 3750 A., and for αβ-unsaturated aldehydes and ketones, between 3800 and 3950 A.

Experimental.

Melting points are uncorrected. Rotations were carried out in a 1 dcm. tube in chloroform solutions. Specimens for analysis were dried at a suitable temperature in a high vacuum for some hours.

Cholestenone.—A solution of cholesterol (10 g.) in dry acetone (120 c.c.) was mixed with aluminium *tert.*-butoxide (12 g.) in dry benzene (300 c.c.) and refluxed for 18 hours. The reaction mixture was washed with 2N-sulphuric acid, water, and sodium bicarbonate solution and the gum obtained after drying and evaporation was heated in a vacuum for an hour at 100°. The residue solidified on cooling and on crystallisation from methyl alcohol (60 c.c.) and ether (30 c.c.) yielded cholestenone (8·6 g.), m. p. 77—81°. This m. p. was raised to 81—82° after adsorption on and fractional elution from alumina. The semicarbazone, prepared by refluxing an alcoholic solution of the ketone for 15 minutes with aqueous alcoholic semicarbazide acetate (10%), was twice crystallised from alcohol–ethyl acetate (1 : 1) and had m. p. 234—235°. Cholestenoneoxime, prepared in a similar manner from hydroxylamine acetate, after crystallisation from ethyl acetate, had m. p. 152—153°. 2 : 4-Dinitrophenylhydrazone : A hot solution of the ketone in alcohol was added to a slight excess of the hydrazine hydrochloride in alcohol. The flocculent red precipitate was collected after 3 hours, washed, dried, and adsorbed on a column of activated alumina from benzene solution. The main red band obtained on developing the chromatogram was washed through with benzene and the solid remaining after evaporation was crystallised from benzene–alcohol (4 : 1), giving the cholestenone-2 : 4-dinitrophenylhydrazone in fine red needles (plates from benzene alone), m. p. 233° (Found : N, 10·4. Calc. for $C_{33}H_{48}O_4N_4$: N, 9·9%).

Fucostadienone.—Fucosterol (10 g.), oxidised as above, gave a ketone which was purified by adsorption on alumina from solution in light petroleum (b. p. 40—60°). Elution with benzene yielded a residue, which was crystallised from methyl alcohol and finally from acetone to give *fucostadienone* (5 g.) in elongated plates, m. p.

94—94·5°, $[\alpha]_D^{20°}$ + 76° (*c* = 1·5) (Found: C, 84·9; H, 11·3. $C_{29}H_{46}O$ requires C, 84·8; H, 11·2%). The *semicarbazone*, crystallised from alcohol–chloroform, had m. p. 238° (decomp.) (Found: N, 9·25. $C_{30}H_{49}ON_3$ requires N, 9·0%). The *oxime* was purified by crystallisation from alcohol and sublimation in a high vacuum, forming needles, m. p. 166—167° (Found: N, 3·3. $C_{29}H_{47}ON$ requires N, 3·3%). The 2 : 4-*dinitrophenylhydrazone* after purification by percolation of a benzene solution through activated alumina separated from benzene in flat needles, m. p. 237° (Found: N, 9·9. $C_{35}H_{50}O_4N_4$ requires N, 9·5%).

Stigmastadienone.—The crude solid from the oxidation of stigmasterol (700 mg., m. p. 166—168°) was dissolved in benzene–light petroleum (b. p. 40—60°) (1 : 1) and fractionated on activated alumina. Ten fractions were collected and from seven of these crystalline material, m. p. 123—125°, was obtained, which after two crystallisations from acetone–methyl alcohol yielded stigmastadienone (400 mg.), m. p. 124·5—125° (Fernholz and Stavely, *loc. cit.*, give m. p. 125°), $[\alpha]_D^{20°}$ + 56° (*c* = 1·59) (lit., $[\alpha]_D^{20°}$ + 63°). The *oxime* was crystallised twice from light petroleum (b. p. 40—60°), separating in needle clusters, m. p. 187—188° (Found: C, 82·0; H, 11·1. $C_{29}H_{47}ON$ requires C, 81·8; H, 11·1%). The semicarbazone was crystallised from alcohol–chloroform (1 : 1) and had m. p. 238—239° (Fernholz and Stavely, *loc. cit.*, give m. p. 235—237°). The 2 : 4-*dinitrophenylhydrazone* after purification by percolation of a benzene solution through activated alumina, crystallised from alcohol–benzene (1 : 1) in fine red needles, m. p. 244—245° (decomp.) (Found: N, 9·3. $C_{35}H_{50}O_4N_4$ requires N, 9·5%).

Sitostenone.—Crude sitosteryl acetate (50 g.) (*ex* wheat germ oil) was crystallised from ethyl acetate in such a manner that the less soluble and the more soluble fractions were eliminated. After 16 crystallisations a β-sitosteryl acetate (10 g.) was obtained, m. p. 125°, $[\alpha]_D^{20°}$ − 35° (*c* = 2·10). On hydrolysis with alcoholic potassium hydroxide, this yielded a β-sitosterol in long flat needles from acetone–alcohol (1 : 1), m. p. 136—137°, $[\alpha]_D^{20°}$ − 32° (*c* = 1·99). Oxidation of this sterol (5 g.) as previously described yielded a pale yellow gum which solidified on cooling. A solution of this in light petroleum (b. p. 40—60°) was run through a column of activated alumina (18 × 2 cm.); by variation of the proportion of benzene in the mixture used to develop the chromatogram, 27 fractions (each of 50 c.c.) were obtained. The product from each of these was crystallised from methyl alcohol and adjacent fractions of similar m. p. were combined and recrystallised from the same solvent. The five main fractions resulting from this procedure, in the order in which they were eluted from the adsorbent, were: (A) m. p. 115—122° (650 mg.); (B) m. p. 95—97° (150 mg.); (C) m. p. 86—88° (450 mg.); (D) m. p. 79—81° (800 mg.); (E) m. p. 131—133° (550 mg.).

Further crystallisation of (A) gave a crystalline solid, m. p. 143—145°, $[\alpha]_D^{20°}$ + 52° (*c* = 1·30). *Light absorption in alcohol:* Maxima, 2405 and 2900 A., $E_{1\,cm.}^{1\%}$ 70 and 2·5 respectively. The 2 : 4-*dinitrophenylhydrazone*, purified by adsorption on and fractional elution from alumina, was obtained as a red amorphous powder from ethyl acetate, m. p. 208—209° (Found: N, 9·0. $C_{35}H_{54}O_4N_4$ requires N, 9·4%). *Light absorption in chloroform:* Maxima, 3730 and 2540 A., $E_{1\,cm.}^{1\%}$ 430 and 265 respectively.

Since fractions (B) and (C) exhibited similar light absorption in alcohol and gave the same 2 : 4-dinitrophenylhydrazone, m. p. 245°, they were combined and twice crystallised from methyl alcohol, yielding a small quantity of a product, m. p. 112—115°, which was not examined further.

Fraction (D) on crystallisation from ethyl alcohol yielded sitostenone, m. p. 83—84° (Found: C, 84·6; H, 11·6. Calc. for $C_{29}H_{48}O$: C, 84·4; H, 11·7%). Prepared in the usual manner and separating from benzene–alcohol (1 : 1) as a dark red powder, the 2 : 4-*dinitrophenylhydrazone* had m. p. 247—248° (Found: N, 9·4. $C_{35}H_{52}O_4N_4$ requires N, 9·45%).

Fraction (E), which required benzene–methyl alcohol (20 : 1) for elution from the alumina, after crystallisation had m. p. 133—134·5°, $[\alpha]_D^{20°}$ − 20·2° (*c* = 1·53).

We wish to record our indebtedness to Professor I. M. Heilbron, D.S.O., F.R.S., for his interest in this work. We are indebted to the Rockefeller Foundation for financial assistance, to the Board of the British Rubber Producers Research Association for a grant to one of us (P. A. W.), and to Dr. G. A. D. Haslewood for a gift of stigmasterol.

Imperial College of Science and Technology, London, S.W. 7. [*Received, February 20th*, 1942.]

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69. *The Self-condensation of Acetylcyclohexene.*

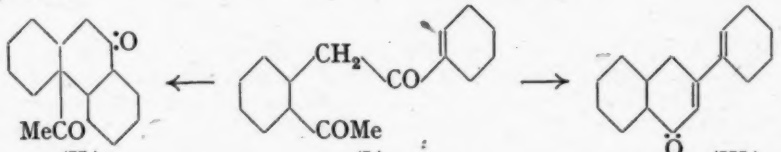
By E. R. H. Jones and H. P. Koch.

The two dimerides formed by the action of sodamide on acetyl*cyclo*hexene (Rapson and Robinson, J., 1935, 1285) are stereoisomeric saturated perhydrophenanthrene diketones of structure (II). They both yield phenanthrene on dehydrogenation, show no high intensity absorption in the ultra-violet, and form only monoketonic derivatives. A third self-condensation product has also been isolated for which the constitution 1-*keto*-3-cyclo*hexenyl*-Δ²-*octahydronaphthalene* (III) is proposed, since on dehydrogenation it yields 2-phenylnaphthalene.

In an abortive attempt to condense 2-methyltetralone with acetyl*cyclo*hexene in the presence of sodamide Rapson and Robinson (J., 1935, 1285) observed the formation of two dimerides of the unsaturated ketone

which were assumed to be *cis*- and *trans*-isomerides of structure (I), each yielding one mol. of acetic acid on oxidation by the Kuhn–Roth micro-method. Since we have encountered both isomers, together with yet another self-condensation product, to a greater or lesser extent in a number of experiments involving condensation with acetyl*cyclo*hexene in the presence of sodamide, we have undertaken a more detailed investigation of the constitutions of these compounds.

By the action of sodamide on acetyl*cyclo*hexene in ethereal solution we have isolated, in addition to the two dimerides, m. p.'s 205° and 130°, described by Rapson and Robinson, a third and more soluble compound of m. p. 85°.



(II.) (I.) (III.)

The dimerides of m. p. 205° and 130° form only *monoximes* and *mono*-2 : 4-*dinitrophenylhydrazones*, they exhibit no selective absorption in the ultra-violet of greater intensity than $E^{1\%}_{1\,cm.} = 50$ between 2000 and 3000 A., and on dehydrogenation with selenium, phenanthrene is produced. A diketone of structure (I) would probably yield a dioxime and would certainly exhibit light absorption properties characteristic of an αβ-unsaturated ketone. The two dimerides in question are now to be considered as stereoisomeric α- and β-12-acetyl-9-ketotetradecahydrophenanthrenes (II) respectively, formed by an internal Michael reaction from the hypothetical intermediate diketone (I). Heilbron and his collaborators (J., 1927, 1888; 1928, 2323) obtained saturated dimerides of styryl methyl ketones in the presence of piperidine for which *cyclo*butane structures were suggested. It now seems probable that these compounds (which form only monoketonic derivatives) are similar in type to (II).

The third product of the self-condensation is an unsaturated ketone, $C_{16}H_{22}O$, which has been characterised by the preparation of an *oxime*, m. p. 232° (decomp.), a *semicarbazone*, m. p. 213°, and a 2 : 4-*dinitrophenylhydrazone*, m. p. 228°. The absorption spectra of the ketone and of its three derivatives (see Experimental) provide conclusive evidence that the carbonyl group is conjugated with a diene system and the isolation of 2-phenylnaphthalene on catalytic dehydrogenation of the ketone in the presence of palladium–norit indicates the carbon skeleton. On this evidence it is suggested that this third self-condensation product is 1-*keto*-3-cyclo*hexenyl*-Δ^2-*octahydronaphthalene* (III) produced by the intramolecular aldol condensation of the intermediate diketone (I), the latter reaction finding analogies in the intramolecular cyclisation of azafrinone to anhydroazafrinone (Kuhn and Brockmann, *Annalen*, 1935, **516**, 95) and of capsanthinone to anhydrocapsanthinone (Zechmeister and von Cholnoky, *ibid.*, 1936, **523**, 101). The self-condensation of β-methylcrotonaldehyde to 4 : 6 : 6-trimethyl-$\Delta^{1:3}$-*cyclo*hexadien-1-al (Fischer and Lowenberg, *ibid.*, 1932, **494**, 263) presumably takes place by a similar series of reactions.

1-Acetyl-2-methyl*cyclo*hexene does not undergo self-condensation when treated with sodamide in ethereal solution.

Experimental.

Self-condensation of 1-*Acetyl*cyclo*hexene.*—1-Acetyl*cyclo*hexene (44 g.) (Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, 1931, **14**, 1157) was stirred with sodamide (10 g.) in dry ether (1000 c.c.) for 18 hours at 20° and was then refluxed for 2 hours. The product was isolated in the usual manner after addition of ice and ammonium chloride and on distillation gave a small quantity of starting material (2 g.) and then a viscous gum (32 g.), b. p. 160—170°/0·05 mm., which did not crystallise spontaneously even after long standing. Trituration with light petroleum (b. p. 40—60°) gave a solid (A) (16 g.), m. p. 122—127°, and evaporation of the petroleum solution gave a residue (B) which crystallised partially on standing for some hours at 0°.

α-12-*Acetyl*-9-*ketotetradecahydrophenanthrene* (II).—Repeated crystallisation of the solid (A) from alcohol gave the α-isomer (2·5 g.) in fine needles, m. p. 205° (Robinson and Rapson, *loc. cit.*, give m. p. 205—206°) (Found: C, 77·3; H, 10·0. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·8%). The substance contained no active hydrogen (Zerewitinoff) and showed no absorption in the ultra-violet greater than $E^{1\%}_{1\,cm.} = 50$, between 2000 and 3000 A. *Monoxime:* Prepared in the usual manner, this separated from alcohol in fine needles, m. p. 251° (decomp.) (Found: N, 5·4. $C_{16}H_{25}O_2N$ requires N, 5·3%). Oximation in pyridine solution gave the same oxime, m. p. 254° (decomp.), undepressed on admixture with the above specimen (Found: N, 5·2%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in yellow micro-needles, m. p. 293° (Found: N, 12·4. $C_{22}H_{26}O_5N_4$ requires N, 13·1%). *Light absorption in alcohol:* Maximum, 3700 A.; log ε = 4·38.

Dehydrogenation of the α-*Dimeride.*—A mixture of the α-dimeride (2·4 g.) and selenium (3 g.) was heated for 24 hours at 300° and a light petroleum (b. p. 40—60°) extract of the product was percolated through a column of alumina. Evaporation of the eluate yielded a solid (200 mg.) which on crystallisation from aqueous methyl alcohol (90%) yielded phenanthrene, m. p. 98° (picrate, m. p. 144°). These m. p.'s were not depressed by authentic specimens.

β-12-*Acetyl*-9-*ketotetradecahydrophenanthrene* (II).—After removal of the less soluble α-dimeride from the solid (A) the residue (12 g.), when crystallised from petroleum (b. p. 80—100°), gave the β-dimeride (9·5 g.) in fine needles, m. p. 130° (Robinson and Rapson, *loc. cit.*, gave m. p. 126—127°) (Found: C, 77·5; H, 9·8. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·8%). This substance exhibited no absorption in the ultra-violet greater than $E^{1\%}_{1cm.} = 50$, between 2000 and 3000 A. *Monoxime:* Prepared in the usual manner, this separated from aqueous alcohol (75%) in clusters of fine needles, m. p. about 250° (decomp.). Mixed with the oxime of the α-dimeride, it had m. p. 240° (decomp.) (Found: N, 5·2. $C_{16}H_{25}O_2N$ requires N, 5·3%). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous alcohol (85%) as an orange micro-crystalline powder, m. p. 212—213° (Found: N, 13·7. $C_{22}H_{28}O_5N_4$ requires N, 13·1%). *Light absorption in alcohol:* Maximum, 3680 A.; log ε = 4·42.

Dehydrogenation of the β-*Dimeride.*—The β-dimeride (7 g.) was heated with selenium (12 g.) for 24 hours at 350°, the residue was thoroughly extracted with ether, and the gum obtained on evaporation of the ethereal solution was dissolved in benzene–light petroleum (b. p. 40—60°) (1 : 1) and percolated through a column of alumina. Evaporation of the eluate gave a white residue (3 g.) which contained a trace of a hydrocarbon insoluble in light petroleum (b. p. 40—60°) and alcohol but which crystallised from benzene in fine matted needles, m. p. 306°. This material exhibited light absorption properties characteristic of a highly condensed polycyclic hydrocarbon. The main bulk of the product (2·3 g.) had m. p. 60—80°, and resisted further purification by either chromatography or crystallisation but readily yielded phenanthrene picrate, m. p. 144°, from which phenanthrene (0·7 g.), m. p. 98°, was regenerated. Neither the picrate nor the hydrocarbon gave any depression in m. p. on admixture with authentic specimens.

1-*Keto*-3-cyclo*hexenyl*-Δ^2-*octahydronaphthalene* (III).—A solution of the semi-solid material (B) in light petroleum (b. p. 40—60°) was percolated through a column of alumina and evaporation of the eluate yielded a solid which on crystallisation from aqueous methyl alcohol gave 1-*keto*-3-cyclo*hexenyl*-Δ^2-*octahydrophenanthrene* (4 g.) in flakes, m. p. 85° (Found: C, 83·6; H, 9·8. $C_{16}H_{22}O$ requires C, 83·5; H, 9·6%). *Light absorption in alcohol:* Maximum, 2815 A.; log ε = 4·25. The *oxime*, prepared in the usual manner, separated from alcohol in needles, m. p. 232° (decomp.) (Found: N, 5·75. $C_{16}H_{23}ON$ requires N, 5·7%). *Light absorption in alcohol:* Maximum, 2760 A.; log ε = 4·41. The *semicarbazone* was obtained from aqueous alcohol (85%) as an amorphous powder, m. p. 213° (Found: N, 14·6. $C_{17}H_{25}ON_3$ requires N, 14·6%). *Light absorption in alcohol:* Maximum, 3000 A.; log ε = 4·40. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in red microcrystals, m. p. 228° (Found: N, 13·8. $C_{22}H_{26}O_4N_4$ requires N, 13·7%). *Light absorption in alcohol:* Maximum, 3980 A.; log ε = 4·53.

Dehydrogenation of 1-*Keto*-3-cyclo*hexenyl*-Δ^2-*octahydronaphthalene.*—Extensive decomposition occurred on attempted selenium dehydrogenation. The ketone (460 mg.) and palladium–norit (400 mg.; 10%) were heated at 340° in an atmosphere of carbon dioxide, the hydrogen evolved being collected in a nitrometer. After 2 hours 90% of the theoretical amount of hydrogen had been collected and the reaction mixture was cooled and extracted with ether. After being washed with aqueous sodium hydroxide, the ethereal solution was dried and evaporated and a solution of the residual solid in benzene–light petroleum (b. p. 40—60°) (1 : 1) was passed through an alumina column. The eluate was evaporated, and the residual solid purified further by readsorption on alumina from light petroleum solution. Crystallisation of the final residue (90 mg.) from methyl alcohol gave 2-phenylnaphthalene, m. p. 100°, undepressed by an authentic specimen.

The authors express their thanks to Professor I. M. Heilbron, D.S.O., F.R.S., for his interest in this work and to the University of London for the award of a Postgraduate Studentship.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W. 7. [*Received, February 20th,* 1942.]

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70. *A Synthesis of "Heavy" dl-Adrenaline.*

By G. R. CLEMO and G. A. SWAN.

All six hydrogen atoms of the catechol molecule exchange with deuterium oxide in alkaline solution, although replacement of the last is a very slow reaction. *dl*-Adrenaline containing 90% of its hydrogen atoms "heavy" has been prepared; its physiological action is almost indistinguishable from that of "light" *dl*-adrenaline.

DEUTERIUM has been used as an indicator in many biological experiments and it has always been assumed that the substitution of deuterium for protium causes no change in the physiological action of the compound concerned. There is no reason to doubt the validity of this assumption, in general, although the majority of the substances examined (*e.g.*, fats in the metabolic studies of Schoenheimer and Rittenberg) are in the nature of foods, rather than compounds of specific physiological action. However, Erlenmeyr and Lobeck (*Helv. Chim. Acta*, 1937, **20**, 142) prepared acetylcholine bromide in which the hydrogen atoms of the acetyl group were replaced by deuterium atoms; and found the product to be slightly less active physiologically than the corresponding "light" compound. We therefore thought it would be interesting

to attempt the preparation of a substance with marked physiological action in which all, or, at any rate, the greater part of the hydrogen was "heavy," and adrenaline was chosen for the experiment.

For this, "*heavy*" *catechol* was required. Although the exchange reactions of deuterium oxide with phenol (Ingold, Raisin, and Wilson, J., 1936, 1637) and with quinol, resorcinol, pyrogallol and phloroglucinol (Münzberg, *Z. physikal. Chem.*, 1936, *B*, **33**, 23, 39; Geib, *ibid.*, 1937, *A*, **180**, 211) have already been studied, the case of catechol appears not to have been examined. The exchange reaction between deuterium oxide and catechol in alkaline solution was therefore investigated in a qualitative manner. All six hydrogen atoms of the catechol molecule are exchangeable, as was to be expected in view of the fact that each of the four nuclear hydrogen atoms stands in either the *o*- or the *p*-position to a hydroxyl group; but the attainment of equilibrium when all six have been replaced is very slow. Although a specimen of catechol containing 93 atoms % of its hydrogen in the form of deuterium has been obtained, the material which was used in the preparation of "heavy" adrenaline had a deuterium content of only 82 atoms % (*i.e.*, it approximated to the formula $C_6HD_5O_2$).

The "heavy" catechol was condensed with chlorodideuteroacetic deuteracid (prepared by the chlorination of trideuteroacetic deuteracid) to give "heavy" chloroacetocatechol containing 85·5 atoms % of deuterium (cf. Dzierzgovski, *J. Russ. Phys. Chem. Soc.*, 1893, **25**, 154). By treatment of this with a solution of trideuteromethyldideuteramine in deuterium oxide, "heavy" adrenalone was obtained (cf. Dakin, *Proc. Roy. Soc.*, 1905, *B*, **76**, 491). The sulphate of this base, in deuterium oxide solution, was reduced with deuterium in the presence of palladium–charcoal catalyst (Fig. 1); the resulting "heavy" *dl*-adrenaline contained 90 atoms % of deuterium (corresponding to the formula $C_9H_{1\cdot3}D_{11\cdot7}O_3N$).

Dr. J. Secker kindly carried out a physiological test on the product. Injection into a cat produced an elevation of blood pressure almost indistinguishable from that produced by a similar amount of "light" *dl*-adrenaline (Fig. 2). It is concluded that the replacement of protium by deuterium in adrenaline causes little (if any) change in the physiological action.

Experimental.

The isotopic analyses were carried out in the way described in this vol., p. 371.

Except where otherwise stated, the deuterium oxide used contained 99·6 atoms % of deuterium.

"*Heavy*" *Catechol.*—Catechol (0·5 g.) was placed in a bulb-tube, and deuterium oxide (1 g.) with sodium deuteroxide (5 mg. approx.) added; the cooled bulb was evacuated and sealed. After being heated for 4 days at 100°, the tube was cooled and opened, and the water (now only partially "heavy") distilled in a vacuum. A further quantity of deuterium oxide (1 g.) was added, and the above procedure repeated three times. The final residue was extracted with anhydrous ether, the extract dried with anhydrous sodium sulphate, the ether removed, and the residual "*heavy*" *catechol* recrystallised from anhydrous light petroleum (b. p. 80—100°); m. p. 104° (Found: C, 62·8; water, 50·2. $C_6HD_5O_2$ requires C, 62·6; water, 51·3%; isotopic analysis, 82 atoms % D). The water distilled in the exchange reactions contained a little catechol, and was used (instead of 99·6% D_2O) for the first two stages of the subsequent preparation. Thus, on an average, approximately 2 g. of 99·6% deuterium oxide were used for each 0·5 g. of catechol.

By raising the reaction temperature from 100° to 200°, allowing 7 days instead of 4 days at each stage, and by subliming (not extracting or recrystallising) the product, a specimen of "heavy" catechol was obtained which gave an isotopic analysis of 93 atoms % D.

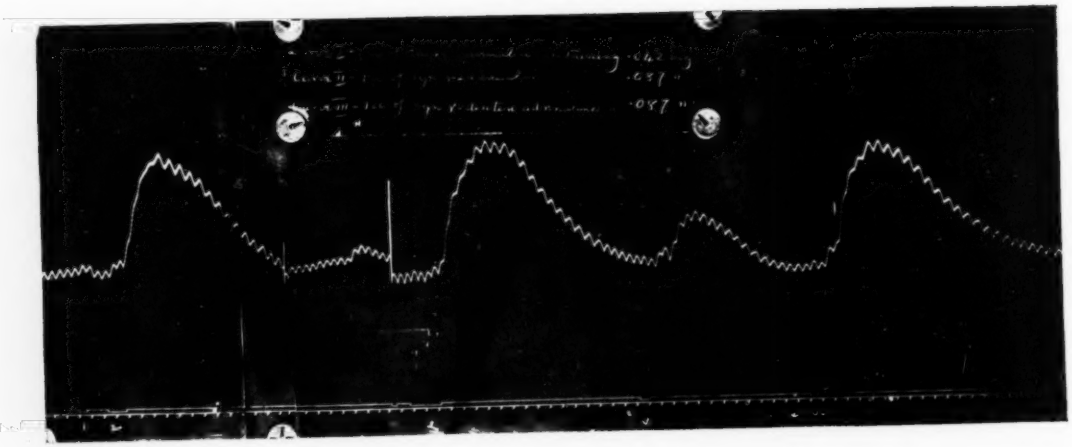
Chlorodideuteroacetic Deuteracid.—Trideuteroacetic deuteracid was chlorinated in the presence of an iodine-red phosphorus catalyst, while being heated on the water-bath. On fractionation, the distillate of b. p. 180—190° crystallised on cooling, giving chlorodideuteroacetic deuteracid, from which the remaining iodine was removed by standing over potash in a vacuum (isotopic analysis, 92 atoms % D).

"*Heavy*" *Chloroacetocatechol.*—Freshly distilled phosphoryl chloride was redistilled from a little quinoline (to remove hydrogen chloride), and the product fractionated out of contact with moisture. "Heavy" catechol of deuterium content 82 atoms % (0·12 g.), chlorodideuteroacetic deuteracid (0·11 g.), and purified phosphoryl chloride (0·08 g.) were heated together for 8 hours at 55—60°. Hot deuterium oxide (1·3 g.) was then added and, after the solution had been kept overnight in the refrigerator, the "heavy" chloroacetocatechol (0·06 g.) was collected, washed with deuterium oxide, and dried. When recrystallised from deuterium oxide, it had m. p. 172° (isotopic analysis, 85·5 atoms % D).

"*Heavy*" *Adrenalone.*—The above "heavy" chloroacetocatechol (0·12 g.) was mixed thoroughly with a solution of trideuteromethyldideuteramine (24%) in deuterium oxide (0·35 g.) and kept for 2 days at room temperature. The crude product (0·07 g.) was collected, and washed with deuterium oxide until the washings were no longer coloured. It was dissolved in a small volume of a hot dilute solution of "heavy" sulphuric acid in deuterium oxide, filtered while hot, and allowed to cool; "heavy" adrenalone sulphate then crystallised, and was collected, washed with a little ethyl deuteralcohol (prepared by the method of Erlenmeyr, Schenkel, and Epprecht, *Helv. Chim. Acta*, 1937, **20**, 368), and dried. The mother-liquors yielded a further quantity of this material on the addition of ethyl deuteralcohol, followed by anhydrous ether.

"*Heavy*" dl-*Adrenaline.*—The deuterium gas for the reduction was generated by the action of deuterium oxide on clean sodium in the apparatus illustrated in Fig. 1. The glass bulbs 10 and 11 of capacity 250 c.c.

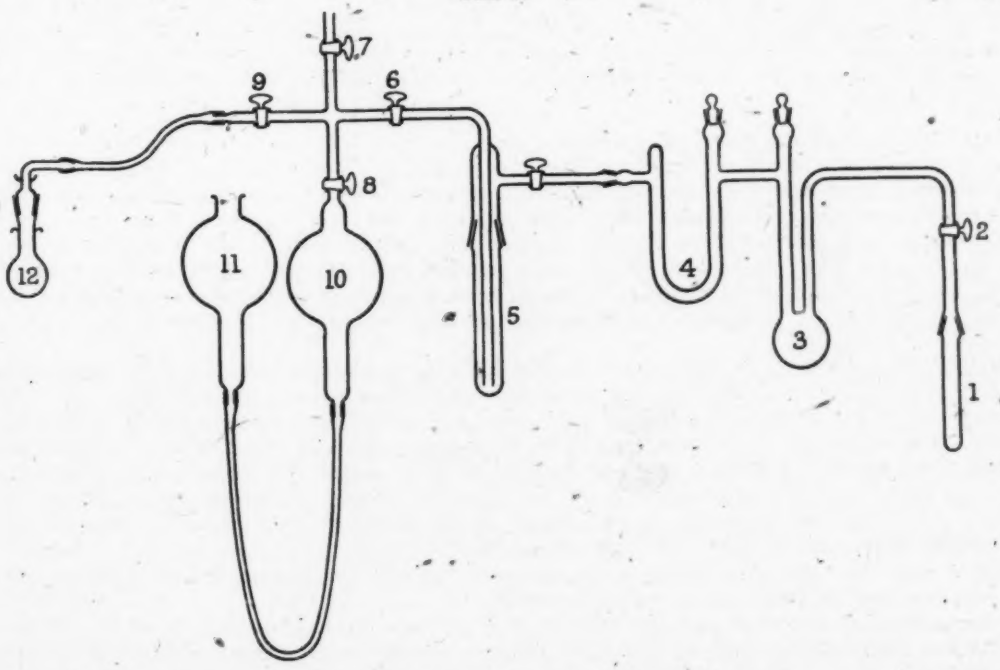
FIG. 2.



[*To face p.* 397.

contained mercury, and clean sodium was introduced into the vessels 3 and 4. Deuterium oxide (approximately 0·6 g.) was placed in tube 1, and cooled strongly while the apparatus was exhausted by means of a high-vacuum pump connected at 7. Then vessel 3 was cooled in solid carbon dioxide–alcohol, and tube 1 allowed to warm so that the deuterium oxide distilled over into vessel 3. When the latter was allowed to warm, reaction occurred; the evolved deuterium was collected in the bulb 10 (trap 5 being cooled in liquid air). The reduction vessel

FIG. 1.



12, which could be shaken mechanically, was of capacity 5 c.c. and was connected to the deuterium storage vessel by a length of "aged" rubber pressure tubing. The palladium–charcoal (10%) was heated for 1 hour at 80°/15 mm. to remove as much as possible of the adsorbed moisture.

"Heavy" adrenalone sulphate (16 mg.) was dissolved in deuterium oxide (1·1 g.), palladium–charcoal (3 mg.) added, and the mixture shaken in an atmosphere of deuterium for 15 hours. The catalyst was then removed, and washed with a little deuterium oxide. To the filtrate was added a slight excess of anhydrous sodium carbonate; the separation of the product soon commenced. After standing for 2 hours out of contact with air, the "heavy" *dl*-adrenaline (10 mg.) was collected, washed with deuterium oxide, and dried in a vacuum desiccator. It formed a white powder, m. p. 208° (isotopic analysis, 90 atoms % D).

Physiological Test.—"Light" *dl*-adrenaline was prepared in a similar way to the "heavy" compound; and an aqueous solution of the sulphate prepared containing 1·74 mg. of the base per 10 c.c. 1·74 Mg. of the "heavy" base were weighed out into a 10 c.c. graduated flask, and dissolved in approximately 0·2 c.c. of deuterium oxide containing sufficient "heavy" sulphuric acid to neutralise the base. Meanwhile a cat was anæsthetised with "Dial" liquid compound; and prepared so that injections could be made into the femoral vein, while the arterial blood pressure could be continuously recorded. Fig. 2 shows the tracings obtained. The first peak (on the left) was obtained by injection of Bayer (optically active) adrenaline; after the canula had been washed out with saline, 0·5 c.c. of the "light" adrenaline solution was injected, followed by 2 c.c. of 0·9% sodium chloride solution (second peak). A further 2 c.c. of saline were then run in, to wash out the canula, leading to a slight rise in pressure, represented by the small peak. Then the "heavy" adrenaline (until now in deuterium oxide solution) was made up to 10 c.c. with "light" water, and 0·5 c.c. of the resulting solution immediately injected, followed by 2 c.c. of 0·9% sodium chloride solution. The resulting increase in blood pressure (last peak) was almost identical with that produced by the "light" *dl*-adrenaline. It was thus concluded that the physiological actions of *dl*-adrenaline, $C_9H_{13}O_3N$, and "heavy" *dl*-adrenaline, $C_9H_{1\cdot3}D_{11\cdot7}O_3N$, are approximately equal.

Our thanks are due to Imperial Chemical Industries Ltd. for a grant towards the purchase of deuterium oxide and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (G. A. S.).

UNIVERSITY OF DURHAM, KING'S COLLEGE, NEWCASTLE-UPON-TYNE. [*Received, February 21st*, 1942.]

71. *Rare-earth Metal Amalgams. Part I. The Reaction between Sodium Amalgam and Rare-earth Acetate and Chloride Solutions.*

By Joseph K. Marsh.

Samarium, europium, and ytterbium in acid acetate solution pass into the mercury when shaken with dilute sodium amalgam. The reaction gives an efficient means of separating various rare-earth elements. The cerium-group elements all show a lower power of amalgam formation, which decreases in order of atomic number. Higher amalgam yield but lower efficiency has been attained by the use of acid chloride solutions. Europium amalgam and hydrochloric acid give solid europous chloride, but this salt did not exchange metal quantitatively with sodium amalgam. A soluble europous hydroxide results from the action of water on europium amalgam.

Rare-earth metal amalgams have hitherto been studied chiefly with a view to the preparation of the metals. Jukkola, Audrieth, and Hopkins (*J. Amer. Chem. Soc.*, 1934, **56**, 303) electrolysed anhydrous chlorides in alcoholic solution and obtained 1—3% of lanthanum, cerium, neodymium, and samarium in mercury, and 0·2% of yttrium. West and Hopkins (*ibid.*, 1935, **57**, 2185) found it simpler to treat the solutions with sodium amalgam, and obtained 2—2·5% yttrium amalgam, but failed to prepare amalgams in presence of water. McCoy (*ibid.*, 1941, **63**, 1622, 3432), however, prepared europium, ytterbium, and samarium amalgams in 95, 22, and 13% yields by electrolysis of aqueous acetate solutions in presence of potassium citrate and carbonate, and found that potassium and sodium amalgams react with acetate–citrate solutions to produce rare-earth metal amalgams.

The author has treated rare-earth solutions, generally the acetate, with dilute sodium amalgam under acid conditions: there is rapid reaction between the sodium and acid with production of nascent hydrogen, and despite such loss of sodium the efficiency is greater than that obtained by more gentle reaction in alkaline solution or by electrolysis. The present work is only preliminary, but indicates that 100% amalgam formation is obtainable by treating europium, samarium, and ytterbium acetate solutions with a weight of sodium equal to that of the rare-earth oxide. This represents an efficiency of 25—30% for the reaction $3Na + E^{\cdots} \longrightarrow E + 3Na^{\cdot}$. In addition to these three earths, which have well-known bivalent states, other earths can be made to afford amalgams by this very vigorous reducing reaction. The yields fell with increasing atomic number and were insignificant on reaching gadolinium, but with lanthanum, cerium, praseodymium, and neodymium considerable amalgam formation occurred.

In the case of the acetates, the exchange of metal is soon brought to a balance as sodium acetate accumulates in the solution. With concentrated lanthanum chloride solution and a large amount of sodium, the solubility of sodium chloride set a limit to the accumulation of sodium in solution and this made possible the extraction of nearly all the lanthanum before the solution became too full of solid sodium chloride for further work.

The applications of amalgam formation to practical problems of separations of the rare earths appear promising. The author has found that traces of europium and samarium may be separated from gadolinium; that a samarium–gadolinium mixture can be resolved immediately into nearly pure components; that a crude yttrium earth can have removed in one operation most of the europium, samarium, and ytterbium, and that lutecium containing a little ytterbium can have this removed in one operation.

The efficiency of the separation of the rare earths from one another by amalgam formation appears to be better than that obtained by reductions to salts in the bivalent state. The separation of the amalgam layer from the aqueous layer at the end of a reaction is more satisfactory than removal of a precipitated salt which retains mother-liquor or is subject to reoxidation, and may itself not be entirely insoluble. The comparative merits of reduction of ytterbium sulphate (Marsh, J., 1937, 1367) and of formation of ytterbium amalgam as a means of preparing pure ytterbium or lutecium salts from their mixture is a case in point. The operations are simple, and no element difficult to remove is introduced. The individuality of the elements appears to be retained more than sometimes occurs in mixed earths, and application of the process to the removal of traces of impurities is very satisfactory.

Another feature of interest is the readiness of samarium to form an amalgam. Although the bivalent samarium salts are less stable than ytterbous salts, the amalgam-forming power of samarium is probably superior to that of ytterbium. Bivalent salts or ions can be produced in solution by the action of sodium amalgam on tervalent salts, as shown by the production of the coloured (Sm and Yb) or colourless (Eu) bivalent solutions. In chemical reactivity samarium, europium, and ytterbium amalgams are much superior to the cerium-group metal amalgams: either there is a difference in combining power with mercury, or the two groups of metals may exist in different valency states in mercury. The stability of the cerium-group metals favours the theory that these exist in a tervalent condition, the other three metals resembling the alkaline-earth metals in reactivity. Klemm and Bommer, and Bommer and Hohmann (*Z. anorg. Chem.*, 1937, **231**, 138; 1939, **241**, 268) conclude from atomic-volume determinations that europium, ytterbium, and to some extent samarium, exist normally in the metallic state in a bivalent condition. This probably holds true also in amalgams.

Good evidence that the cerium-group elements can give rise to bivalent salts has been obtained by Holleck and Noddack (*Angew. Chem.*, 1937, **50**, 819), who stabilised a proportion of bivalent sulphate by entrainment

with strontium sulphate when strontium amalgam acted on saturated rare-earth sulphate solutions. They concluded that the stability of the bivalent state can be gauged by the proportion of bi- and ter-valent sulphate found. Their results are in line with those of Noddack and Brukl (*ibid.*, p. 362), who measured reduction potentials by polarographic means and gauged the stability of the bivalent state by the difference between the discharge potentials for bivalency and for metal formation. Measured by either method, the elements fall into the same order of bivalent stability (Table I, *a* and *b*). Holleck and Noddack's results,

TABLE I.

(*a*) % of rare-earth sulphate found in bivalent state (H. and N.).
(*b*) P.D. (volts) between $E''' \longrightarrow E''$, and $E''' \longrightarrow$ metal formation (N. and B.).
(*c*) Amounts (mg.) of E_2O_3 *ex* bivalent sulphate from reduction of 50 ml. of saturated $E_2(SO_4)_3$ with strontium amalgam (H. and N.).
(*d*) Relative amalgam forming power (see Table II).

	La.	Ce.	Pr.	Nd.	Sm.	Eu.	Gd.	Yb.
(*a*)		4	5·4	4·6	70	90	15	80
(*b*)	0·105	0·105	0·115	0·090	0·290	1·80	0·145	0·575
(*c*)		16	21	19	75	59	5	1224
(*d*)	284	273	129	104	980	950	2	960

however, suffer from the defect that different amounts of rare-earth sulphate were used in each experiment. Neither the percentage of bivalent sulphate nor the total bivalent sulphate production is a strictly comparable quantity, but if the latter is taken (Table I, *c*) instead of the former (Table I, *a*) it will be seen that output is roughly parallel to amalgam-forming power.

In the tervalent rare-earth salts, basic strength falls from lanthanum to lutecium, and in a bivalent condition it might be expected that the same would hold true, but that the strength would be much greater and comparable to that of alkaline-earth elements. Similarity of chemical properties and cases of isomorphism between europous and barium and strontium compounds have been proved (McCoy, *J. Amer. Chem. Soc.*, 1937, **59**, 1132). It has long been known that alkaline-earth ions in solution and alkali metals in amalgam are reversibly replaceable (Smith, *Amer. Chem. J.*, 1907, **37**, 506), but it has not hitherto been regarded as possible to effect an exchange between alkali-metal amalgams and tervalent ions in solution. The attempt results in the reaction of the sodium with hydrogen ions in preference to the tervalent ions, and only hydrogen is produced. If, however, certain tervalent rare-earth metal salts in solutions of suitable p_H are treated with sodium amalgam, the metal now gains the power, usually confined to uni- and bi-valent metals, of exchanging with the sodium in amalgam. The conditions found necessary favour a high concentration of nascent hydrogen at a surface of high overvoltage. The three rare-earth elements with well-known bivalent states are those which can most easily form amalgams. Less acid conditions are required than in the case of the other earths, but it seems reasonable to postulate that a bivalent state precedes amalgam formation in all cases. If the bivalent state is very unstable, high concentrations of nascent hydrogen must be maintained in order to produce a sufficient concentration of bivalent ions to effect an exchange with the sodium in amalgam; but much hydrogen gas will result at the same time. To remove a valency electron becomes progressively more difficult as the lanthanide contraction grows in mounting the rare-earth series, and it is almost impossible when gadolinium is reached.

EXPERIMENTAL.

Preparation of Acetates.—The oxides were dissolved in acetic acid, and the salt crystallised. Ytterbia and lutecia required several hours' digestion with excess of hot 30% acid to effect solution. Samples of acetates were ignited to oxide, which was weighed.

Preparation of Sodium Amalgam.—Sodium slices (25 g.) were added to warm mercury (975 g.). The hot, liquid amalgam was poured into test-tubes, which were corked and at once laid flat. Easily crushed crystalline sticks resulted. When required, a portion was weighed, crushed, and added with 1 drop of water to pure mercury.

" Extraction " by Sodium Amalgam.—It will be convenient to refer to the reaction between sodium amalgam and rare-earth solutions, whereby rare-earth metal amalgams are formed, as a process of extraction. The reaction was carried out by shaking in an extraction funnel. The rare-earth element passed from the aqueous to the mercury layer, and those elements which can form amalgams were thereby extracted from those which cannot.

Effect of Dilution on Amalgam Formation.—(a) *Lanthanum.* 1 G. of lanthana was dissolved in hydrochloric acid, diluted to 5 ml., and brought into reaction with (1) 40 g. of 1·25% sodium amalgam or (2) 200 g. of 0·25% amalgam; (3) before treatment as in (2) the acid solution was diluted to 50 ml. The mixture was shaken in a separating funnel and kept slightly acid by addition of drops of concentrated hydrochloric acid. When the sodium was exhausted, the mercury was run through water in another funnel and then shaken with concentrated hydrochloric acid in a third funnel till calomel began to form. Most of the excess acid was removed by evaporation, the solution diluted, and the lanthanum precipitated with oxalic acid. Yields of oxide: (1) 44, (2) 77, (3) 90 mg.

(b) *Samarium.* 1 G. of samaria, similarly treated, gave yields of oxide: (1) 185, (2) 218, (3) 127 mg.

Extraction of Lanthanum Chloride Solution.—1 G. of lanthana was made into 8 ml. of chloride solution and treated with three portions of sodium amalgam (total 5·7 g. of sodium in 25 ml. of mercury). Concentrated hydrochloric acid was added to keep the solution acid. The reaction went vigorously at the b. p. There remained in the chloride solution only 13% of the lanthanum, as found by precipitation as hydroxide, then as oxalate, and subsequent ignition of the oxalate.

Similar experiments with praseodymium chloride (1·5 g. + 3 g. of sodium in 15 ml. of mercury) and neodymium chloride (1·5 g., 4 g., and 20 ml. respectively) yielded 210 mg. of praseodymium oxide and 70 mg. of neodymium oxide on treating the amalgams with concentrated hydrochloric acid, precipitaing the extract with oxalic acid, and igniting the oxalate.

Extraction of Samarium Chloride Solution.—1 G. of samaria was made into chloride solution and shaken with 100-g. portions of 1% sodium amalgam four times. Reaction of the first two lots produced a deep red-brown colour in the chloride solution due to $Sm^{\cdot\cdot}$ ions. The yields (mg.) of oxide from the extracts were: (1) 390, (2) 340, (3) 116, (4) 15. The residue recovered from the chloride solution was 22 mg.

Yttrium and terbium chloride solutions treated similarly gave only traces of amalgam formation.

Use of Acetate Solutions.—Better extraction was obtained initially by using acetate solutions and acetic acid, but after 1 g. of sodium had accumulated in 10 ml. of solution little further progress could be made. When chloride solutions were used, the precipitation of sodium chloride set a limit to the sodium concentration, so some rare-earth extraction could still take place. Sodium acetate, on the other hand, sometimes salted out the rare-earth acetate.

Comparative Reducibility of Rare-earth Acetates.—The standard experiment was performed as follows. Rare earth in the form of neutral acetate dissolved in 10 ml. of water was treated with 20 g. of 2·5% sodium amalgam + 15 ml. of mercury. The solution and amalgam were shaken continuously with a rotatory motion in a 100-ml. conical tap funnel, drops of glacial acetic acid being added from a burette to keep the solution acid. A cloud of small hydrogen bubbles made the solution milky, and the rate of reaction was better judged by ear than by eye. Brisk effervescence promoted amalgam formation. A p_H of 4—5 was probably the most favourable, but in presence of bivalent salts or nascent hydrogen the B.D.H. universal indicator was bleached, and so could only be used before or after the reaction. The total addition of acetic acid varied from 0·4 ml. in the case of the strongly bivalent earths to 1·4 ml. when little amalgam formation occurred, and nearly all the sodium reacted with the acid. The temperature had but little influence: it was generally above rather than below 50°. The reaction generates considerable heat. The reaction time depended upon the rate of addition of the acetic acid. Yields were optimum at 3—5 mins. At the conclusion of the reaction the amalgam was run off, washed by passing through water in another tap funnel, and then decomposed in a third funnel. The rare-earth metal amalgams react only slowly with water at the concentrations here prepared, so that by running a portion of the mercury into water it could be seen at once approximately how much sodium, if any, was still present. A series of experiments according to this procedure was carried out with a variety of earths. A second extraction was usually made in the same way, but never gave more than 20% of the yield of the first, and when third extractions were attempted they proved fruitless. Unreduced residues of samarium, europium, and ytterbium were recovered by precipitation with ammonia. The collected hydroxide was dissolved in nitric acid, and the earth precipitated as oxalate and ignited. In each case the residue proved to be composed at least in large part of less easily reduced earths originally present as impurity. The results are collected in Table II.

TABLE II.

Comparative reducibility of rare-earth acetates by sodium amalgam. Yields (in mg.) of oxide recovered on treating the equivalent of 1 g. of oxide with 0·5 g. of sodium in 15 ml. of mercury.

	Extract.				Extract.			Extract.	
Element.	1.	2.	Residue.	Element.	1.	2.	Element.	1.	2.
Sm	900	—	75	La	285	20	Nd	113	0·4
	895	—	95		255	—		96	—
	888	88	2·5		255	8	Gd	2	—
Eu	894	25	5	Ce	248	49		2	—
	933	15	4·5		244	4	Dy	0·5	—
	931	34	4·4	Pr	108	0·5		0·4	—
Yb.....	704	265	18		150	—	Yt	0·4	—
	810	142	23						

Ytterbium amalgam is the least stable; samarium and europium amalgams are a little more stable, but care was necessary with these three elements not to over-run the end-point: it was best to run off the mercury while it still contained a little sodium. Amalgams of lanthanum, cerium, praseodymium, and neodymium are more stable, and in these cases it was best to keep the solution rather more acid and to allow the sodium to react completely.

Very dilute europium, samarium, and ytterbium amalgams, but most readily the last, react peculiarly with water. At first, on shaking, if any sodium amalgam is present this is decomposed; then suddenly on continued shaking the mercury breaks into droplets and forms a sludge, rare-earth hydroxide beginning to appear in suspension. When all of any one of these three metals has reacted, the mercury suddenly coalesces again, but if any cerium-earth metal was present in the amalgam it will still be found there at this juncture. If the amalgams are not dilute the separation from sodium is not quite sharp, the same droplet formation does not occur, but the hydroxide is stained black by admixture with very finely divided mercury. In this case it is better to treat the amalgam with 2N-hydrochloric acid; most of the sodium will still react first and may be fairly sharply separated—any rare earth accompanying it may be precipitated with alkali. For removing the cerium-group metals even more concentrated acid is preferable; shaking is continued until calomel begins to appear, and if the solution is too acid it is then partly evaporated, diluted, and the rare earth precipitated as oxalate.

Ytterbium.—Bivalent ytterbium in solution gives rise to a green colour which deepens to yellow or orange as the concentration rises. When ytterbium amalgam is treated with concentrated hydrochloric acid only a faint transient green is seen, but a strong green colour develops on treatment with 2N-acid. The green colour in acetate solutions treated with sodium amalgam decreases as the solution becomes alkaline and vanishes before precipitation of hydroxide starts. It is restored on addition of acetic acid if there is sufficient ytterbium still in solution. Extraction of ytterbium can take place without the development of any colour. Strong orange tints were produced on treating acetate + citric acid with potassium amalgam, and extraction occurred. Good extraction took place from ytterbium acetate and acetic acid by strontium but not barium amalgam. The reduction of ytterbium requires rather more alkaline conditions than that of the other earth metals. At the end of the run which left the least residue (18 mg.), a p_H of 6·5 was found and much sodium was still present in the mercury. The residues from the ytterbium always showed in the oxide form a reflection band in the green region due to erbium.

Europium.—The material used was known to contain a small amount of neodymium and other earths. The reduced solution was faintly green, possibly due to ytterbium. After the first extraction no absorption bands were visible. Only half the quantity of sodium amalgam was used for the second extraction. The 5 mg. of residue gave strong absorption bands of neodymium, and the oxide was yellow. Low total recoveries of europium were experienced and are ascribed to a loss as $Eu(OH)_2$.

Evidence of a Soluble Europous Hydroxide.—Europium amalgam (30 ml.; about 0·45%) was kept in an open 400-ml. beaker with 60 ml. of water for 40 hours. Much yellow-green hydroxide was formed, and was filtered off. The filtrate was alkaline but quickly bleached methyl-orange. It was boiled and treated with nitric and oxalic acids.

An oxalate precipitate was formed from which 60 mg. of europium oxide were recovered, indicating that europous hydroxide with a solubility of at least 1 g./l. must have been present in solution.

Samarium.—No colour developed in acetate solutions on treatment with amalgams, but by the action of sodium or strontium amalgam on samarium chloride and hydrochloric acid the deep red-brown colour of samarous compounds was developed. The extractions obtained, however, were poor. The colour never persisted for more than 1 minute after withdrawal of the amalgam. The experiment affords a simple demonstration of the bivalency of this element.

Lanthanum.—The low solubility of lanthanum acetate necessitated solution in 25 ml. of water in place of the usual 10 ml.; 25—30% extractions were obtained. A trial in which the solution was kept more faintly acid gave only 18% extraction. The solutions tended to froth and to yield a basic acetate.

Cerium.—15 Ml. of solution were used, and basic salt formation was apt to occur.

Gadolinium.—The 2 mg. yield was examined by arc spectroscopy and found to be mainly gadolinium, but europium and samarium were also present in considerable quantity although the oxide used was supposed to be quite free from these.

Lutecium.—Some oxide from the tail of a bromate fractionation of earths freed as far as possible from ytterbium by precipitation of ytterbous sulphate (Marsh, J., 1937, 1367) gave an extract amounting to 2·8%, and the resulting lutecium oxide showed only two or three of the very strongest ytterbium arc lines.

Samarium–Gadolinium Mixture.—The oxides (5 g.) in acetate solution (50 ml.) were treated three times with 0·5 g. of sodium in 16 ml. of mercury, the successive yields being 300, 118, and 125 mg. of oxide from amalgams. The absorption spectrum of the residue was examined in chloride solution and compared with a standard samarium chloride solution. The samarium content was thus estimated to be 0·3%. The first two extracts appeared to be fairly pure samarium but the absorption spectrum of the third was weak.

Extraction from Crude Yttrium Earths.—A quantity of gadolinite from Iveland, Norway, was opened up, and the resulting rare-earth chlorides treated with potassium sulphate till the absorption spectrum of neodymium could no longer be seen in solution. The resulting yttrium earths were given a single fractional precipitation as ferricyanide. The first precipitate had the highest average atomic weight (115), as found by titration of a sample of oxalate with standard permanganate, and by igniting another sample of oxalate to oxide. 5 G. of the head fraction were made into acetate solution (30 ml.) and treated twice with 0·5 g. of sodium in 16 ml. of mercury, the yields being 33 and 83 mg. (total, 116 mg.). A slight green colour developed for a time. The absorption spectrum of the yield showed considerable samarium, estimated by comparison with standards to be 20 mg. There was just a trace of erbium absorption. The arc spectrum showed much samarium and ytterbium, but only a little europium. Numerous yttrium lines were also seen. A little ytterbium was left with the other earths, but the arc lines were faint compared with those of its scarce neighbour lutecium, which gives a similar type of arc spectrum. The colour of the extracted oxides was the same as that of the original. A pair of strong terbium lines were identified in the extract.

Action of Hydrochloric Acid on Europium Amalgam.—The amalgam from a triple-scale standard experiment was left in contact with 10 ml. of concentrated hydrochloric acid for ½ hour in an atmosphere of carbon dioxide in a tap funnel with occasional shaking. The mercury was then found to be free from europium, which was now in the form of a white salt with a carmine-red fluorescence. The salt was readily soluble in water and had no visible absorption spectrum. The fluorescence was not as strong when the salt was dry, in a carbon dioxide atmosphere or in a vacuum, as when damp and oxidising in air. The salt was dried by warming and attaching the tap funnel to a water-pump. No similar salt was obtained by treating ytterbium or samarium amalgam with concentrated hydrochloric acid.

Attempted Exchange between Sodium Amalgam and Europous Chloride.—The europous chloride (4 g.) just described was dissolved in 10 ml. of water and shaken with 0·25 g. of sodium in 8 ml. of mercury for 10 minutes. Much europium hydroxide was formed, and 0·28 g. of europium oxide was recovered from the amalgam ($EuCl_2 + 2Na \longrightarrow 2NaCl + Eu$ requires 0·945 g.). A similar experiment in which the separation of hydroxide was prevented by addition of acetic acid gave with 3 minutes' shaking 0·451 g. of oxide from the amalgam. The sodium appeared to be exhausted. Neither experiment, therefore, proves satisfactorily that direct exchange of europium for sodium in amalgam can take place without hydrogen formation.

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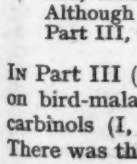
72. *Antiplasmodial Action and Chemical Constitution. Part V. Carbinolamines derived from 6-Methoxyquinoline.*

By HAROLD KING and THOMAS S. WORK.

The aim of this investigation was the search for antiplasmodial substances based on the formula of quinine but of simpler structure. The preparation of a number of unsymmetrical dialkylamines is described and, from these, 1 : 2-carbinolamines have been synthesised containing the 6-methoxyquinoline nucleus. Although the structure of these carbinolamines was very close to that of active antiplasmodials described in Part III, these bases proved to be inactive when tested on bird-malaria in canaries.

IN Part III (King and Work, J., 1940, 1307), it was shown that there was antiplasmodial activity, as tested on bird-malaria in canaries, in the *N*-dibutyl-, -diamyl- and -dihexyl-aminomethyl-6-methoxy-4-quinolylcarbinols (I, R = $CH_2{\cdot}NR_1R_2$). The lower and the higher dialkyl homologues were, however, inactive. There was thus a zone of activity where the sum of the carbon atoms of the *N*-alkyl groups lay between eight and twelve. The present communication describes the synthesis of seven members of a series of secondary amines, in which the groups R_1 and R_2 are different from each other, and their combined carbon atom content is not greater than 12 and not less than 8. It has only been found possible to prepare bases of the structure (I, R = $CH_2{\cdot}NR_1R_2$) from four of these unsymmetrical secondary bases. In the other cases catalytic reduction of the intermediate quinolylketo-bases was followed by fission of the basic group with formation of methyl-6-methoxy-4-quinolylcarbinol (I, R = CH_3).



(I.)

Ethyl-, propyl-, butyl- and *amyl-hexylamines* were prepared by the action of the appropriate alkyl iodides

or bromides on benzylhexylamine. The benzyl group was then removed by catalytic reduction in acetic acid at 70° in the presence of platinum oxide:

$$C_6H_{13}\cdot NH\cdot CH_2Ph + R\cdot Hal \longrightarrow C_6H_{13}\cdot NR\cdot CH_2Ph \longrightarrow C_6H_{13}\cdot NHR + Ph\cdot CH_3$$

In a similar manner *ethyl-* and *propyl-nonylamines* were obtained. Difficulties were, however, encountered in the preparation of *methylnonylamine*. When methyl iodide and *benzylnonylamine* were allowed to react, the products were mainly unchanged base and *benzyldimethylnonylammonium iodide*. This quaternary salt was, however, converted into the hydroxide and then into the hydrosulphide, following Clarke's method (J., 1913, **103**, 1689). On evaporation of the solution of this hydrosulphide under reduced pressure the products were *dimethylnonylamine*, benzylmercaptan and dibenzyl sulphide, the benzyl group showing a preference to be eliminated over the methyl group. This might have been anticipated from the known tendency for benzyl

$$\left[\begin{matrix}Me\\Me\end{matrix}\!\!>\!N\!<\!\begin{matrix}C_9H_{19}\\CH_2Ph\end{matrix}\right]SH \longrightarrow Me_2N\cdot C_9H_{19} + Ph\cdot CH_2\cdot SH + Ph\cdot CH_2\cdot S\cdot S\cdot CH_2Ph$$

groups to be eliminated over other groups in many reactions (compare Snyder and Speck, *J. Amer. Chem. Soc.*, 1939, **61**, 669, 2895, where several references are given). This easy elimination of benzyl groups limits the applicability of Clarke's useful method for the demethylation of quaternary ammonium salts to cases where the benzyl group is absent.

When nonyl iodide and methylamine were allowed to interact in methyl-alcoholic solution at 100°, methylnonylamine was formed, but the main product was *methyldinonylamine*. Methylnonylamine was eventually obtained in good yield by an application of Decker's method. Benzaldehyde and nonylamine were condensed to give *benzylidenenonylamine*, which on methylation gave an oily methiodide. On digestion of the latter with 90% alcohol and treatment with mineral acid benzaldehyde was liberated to ether, and the methylnonylamine recovered from the acid liquor.

The results of the tests on bird malaria due to *Plasmodium relictum* in canaries, of the carbinolamines described in this communication are shown below.

Substance.	Dose in mg. per 20 g. of body weight.	Day of appearance of parasites in blood.	Remarks.
Ethylhexylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 5 *	5	M.T.D.†
	1 × 5 + 5 × 2·5	6	
Propylhexylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 2·5	6	
Butylhexylaminomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 5	5	
Methylnonylaminomethyl-6-methoxy-4-quinolylcarbinol	1 × 2·5 + 5 × 1·25	6	M.T.D.
	1 × 2·5 + 5 × 1·25	6	
2′ : 2′ : 6′-Trimethylpiperidinomethyl-6-methoxy-4-quinolylcarbinol	6 × 5	5	M.T.D.
	6 × 5	5	
Quinine dihydrochloride	6 × 2·5	10	
Control birds		5, 6, 5	

* This means a dose of 5 mg. was given daily for 6 days, the first dose being administered 4 hours after inoculation with malaria.

† M.T.D. = maximum tolerated dose.

In Part III (p. 139) it was found that piperidinomethyl-6-methoxy-4-quinolylcarbinol was inactive on bird malaria. It was thought possible that activity might be restored by bringing up the carbon content to the level shown necessary in the symmetrical secondary bases, that is, between eight and twelve carbon atoms. Accordingly 2′ : 2′ : 6′-trimethylpiperidinomethyl-6-methoxy-4-quinolylcarbinol (I, R = $\cdot N\!<\!\begin{matrix}CMe_2\!-\!CH_2\\CHMe\cdot CH_2\end{matrix}\!>\!CH_2$) was synthesised, but it proved to be without action in the dose shown in the table.

Experimental.

*Benzyl-*n*-hexylamine.*—This base is a by-product in the preparation of benzyldi-*n*-hexylamine (King and Work, J., 1940, 1313). It may be obtained as the main product by the following process: Hexyl bromide (66·0 g.; 1 mol.) and benzylamine (85·6 g.; 2 mols.) after about an hour deposited benzylamine hydrobromide. The mixture was heated on the boiling water-bath for an hour, cooled, and diluted with dry ether, and the benzylamine hydrobromide collected. The ethereal solution was shaken with aqueous sodium hydroxide, dried over potassium hydroxide, then fractionated, giving benzylamine (19·0 g.), b. p. 80—100°/18 mm., benzyl-*n*-hexylamine (51·6 g.), b. p. 142—160°/18 mm. (47 g. on redistillation, b. p. 149—150°/18 mm.; yield, 62% on the hexyl bromide used), and benzyldi-*n*-hexylamine 6·7 g.), b. p. 160—180°/18 mm.

*Benzyl-*n*-butylhexylamine.*—Benzylhexylamine (19·1 g.), *n*-butyl bromide (15·1 g.), and potassium hydroxide (7·7 g.) were heated at 140° for 5 hours. The product was cooled, diluted with aqueous alkali, and extracted with ether. The main non-ethereal fraction (22·75 g.), b. p. 165—171°/18 mm., on refractionation through a column gave *benzyl-*n*-butylhexylamine* (17·4 g.), b. p. 170°/18 mm. (Found: C, 82·7; H, 11·9; N, 5·7. $C_{17}H_{29}N$ requires C, 82·6; H, 11·7; N, 5·7%).

n-*Butylhexylamine.*—Benzylbutylhexylamine (24·7 g.), reduced at 70° (see amyl analogue, below), gave *butylhexylamine* (13·6 g.), b. p. 201°/738 mm. (Found: C, 76·1; H, 14·8; N, 9·0. $C_{10}H_{23}N$ requires C, 76·4; H, 14·6; N, 8·9%). The *hydrochloride* crystallised from acetone in filmy leaflets, m. p. 268° (Found: C, 62·0; H, 12·6. $C_{10}H_{23}N,HCl$ requires C, 62·0; H, 12·5%).

Benzyl-n-amylhexylamine.—Benzylhexylamine (19·1 g.), *n*-amyl bromide (16·6 g.), and potassium hydroxide (17·7 g.) were refluxed at 140° for 3 hours. The mixture obtained in ethereal solution after addition of aqueous caustic alkali gave (1) b. p. up to 100°/15 mm. (hexyl bromide), (2) 5·3 g., b. p. 150—170°/15 mm., (3) 18·0 g., b. p. 170—180°/15 mm. On refractionation (2) and (3) gave *benzyl-n-amylhexylamine* (16·8 g.), b. p. 175—177°/15 mm. (79% yield) (Found: C, 82·3; H, 11·9; N, 5·5. $C_{18}H_{31}N$ requires C, 82·7; H, 12·0; N, 5·4%).

n-*Amylhexylamine.*—Benzylamylhexylamine (26·1 g.) in glacial acetic acid (30 c.c.) and platinum oxide (0·4 g.) was hydrogenated at 70° for 12 hours, and the filtered solution diluted with water and made strongly alkaline. The dried ethereal extract gave n-*amylhexylamine* (14·4 g.), b. p. 108°/15 mm., 216—218°/763 mm. (Found: N, 7·9. $C_{11}H_{25}N$ requires N, 8·2%). The *hydrochloride* separated from acetone in pearly leaflets, m. p. 275—276° (Found: C, 63·8; H 12·4. $C_{11}H_{25}N$,HCl requires C, 63·6; H, 12·6%).

Benzyl-n-propylhexylamine, prepared from benzylhexylamine (19·1 g.), *n*-propyl iodide (17·0 g.), and potassium hydroxide (7·7 g.) at 140° (external bath), had b. p. 149—155°/15 mm. (yield, 20·5 g.) and on refractionation 155°/15 mm. (Found: C, 82·3; H, 11·3; N, 6·2. $C_{16}H_{27}N$ requires C, 82·3; H, 11·7; N, 6·0%).

n-*Propylhexylamine* obtained from benzylpropylhexylamine (34·9 g.) by reduction at 70°, had b. p. 171—181°/753 mm.; yield, 15·4 g. (Found: C, 75·2; H, 15·0; N, 9·5. $C_9H_{21}N$ requires C, 75·5; H, 14·7; N, 9·8%). The very soluble *hydrochloride*, obtained from hydrogen chloride and a low-boiling petroleum solution of the base, crystallised from acetone in pearly leaflets, m. p. 243° (Found: C, 60·2; H, 12·1. $C_9H_{21}N$,HCl requires C, 60·1; H, 12·3%).

Benzylethylhexylamine.—Benzylhexylamine (9·55 g.), ethyl iodide (8·6 g.), and potassium hydroxide (3·85 g.) were heated in sealed tubes at 140—150° for 4 hours. An ethereal extract of the basified product gave *benzylethylhexylamine* (15·6 g.), b. p. 145°/13 mm. (Found: C, 81·9; H, 11·6; N, 6·6. $C_{16}H_{25}N$ requires C, 82·3; H, 11·4; N, 6·4%).

Ethylhexylamine (10·9 g.), obtained from the above base (29 g.) by reduction at 70° and isolated by repeated extraction with ether of the strongly basified mixture, had b. p. 158°/743 mm. (Found: C, 74·2; H, 14·8; N, 10·6. $C_8H_{19}N$ requires C, 74·2; H, 14·8; N, 10·6%). The *hydrochloride* (see propyl analogue) crystallised in pearly leaflets, m. p. 191° (Found: C, 58·2; H, 11·9. $C_8H_{19}N$,HCl requires C, 58·0; H, 12·2%).

Benzyl-n-nonylamine (30·1 g.), obtained from benzylamine (42·8 g.) and nonyl bromide (41·4 g.) (see hexyl analogue), had b. p. 179°/12 mm. (Found: C, 82·0; H, 11·6; N, 6·2. $C_{16}H_{27}N$ requires C, 82·3; H, 11·7; N, 6·0%). *Benzyldinonylamine* (7·0 g.), b. p. 240°/12 mm., was also obtained (Found: C, 83·4; H, 12·3; N, 4·2. $C_{35}H_{65}N$ requires C, 83·5; H, 12·6; N, 3·9%). *Benzylnonylamine hydrochloride* separated from water in needles, m. p. 199—200° (Found: C, 70·9; H, 10·3. $C_{16}H_{27}N$,HCl requires C, 71·2; H, 10·5%).

Benzyl-n-propylnonylamine (32·5 g.), obtained from benzylnonylamine (34·9 g.), *n*-propyl iodide (25·5 g.), and potassium hydroxide (11·5 g.) at 130°, had b. p. 185°/13 mm. (Found: C, 83·4; H, 12·0; N, 5·4. $C_{13}H_{33}N$ requires C, 82·8; H, 12·1; N, 5·1%).

Propylnonylamine (12·3 g.), obtained by reduction of benzylpropylnonylamine (32·5 g.), had b. p. 119°/14 mm. (Found: C, 77·7; H, 14·5. $C_{12}H_{27}N$ requires C, 77·8; H, 14·7%). The *hydrochloride* crystallised from dilute hydrochloric acid in pearly scales, m. p. 237° (Found: C, 64·3; H, 13·0. $C_{12}H_{27}N$,HCl requires C, 64·9; H, 12·7%).

Benzylethylnonylamine.—A mixture of benzylnonylamine (23·3 g.; 1 mol.) and ethyl iodide (17·16 g.; 1 mol.) became warm after 30 minutes and crystals separated. Potassium hydroxide (7·7 g.) was added, the mixture heated on the water-bath for 4 hours, and the product treated with water and ether. The solid (2·2 g.) that separated crystallised from ethyl acetate in white plates, m. p. 64—65°, of *benzyldiethylnonylammonium iodide* (Found: C, 57·2; H, 8·9; N, 3·4. $C_{20}H_{36}NI$ requires C, 57·5; H, 8·7%). The ethereal extract on fractional distillation gave *benzylethylnonylamine* (22·1 g.), b. p. 178°/11 mm. (Found: C, 82·7; H, 11·8. $C_{18}H_{31}N$ requires C, 82·7; H, 12·0%).

Ethylnonylamine (yield, 84·3%), obtained by catalytic reduction of benzylethylnonylamine (22·1 g.) at 70°, had b. p. 103°/14 mm. (Found: C, 77·1; H, 14·5. $C_{11}H_{25}N$ requires C, 77·1; H, 14·7%). The *hydrochloride* crystallised from acetone in pearly leaflets, m. p. 200—201° (Found: C, 63·8; H, 12·6. $C_{11}H_{25}N$,HCl requires C, 63·6; H, 12·6%).

Reaction between Benzylnonylamine and Methyl Iodide.—Benzylnonylamine (16 g.) and methyl iodide (10·7 g.; 1·1 mols.), gradually mixed, reacted vigorously, giving mainly unchanged benzylnonylamine (9·25 g.) and *benzyldimethylnonylammonium iodide*. The latter crystallised from ethyl acetate in plates (4·9 g.), m. p. 89° (Found: C, 54·9; H, 8·3; N, 3·6. $C_{18}H_{32}NI$ requires C, 55·5; H, 8·3; N, 3·6%).

A solution of the methochloride [obtained from the quaternary iodide (14·1 g.)] in water (100 c.c.) was treated with silver oxide, filtered, saturated with hydrogen sulphide, and evaporated to a syrup under reduced pressure at 50°; the residue was re-evaporated three times with a little absolute ethyl alcohol and then heated in a boiling water-bath for 4 hours. The product was now ether-soluble and on fractional distillation gave (*a*) 5·2 g., b. p. 97—99°/14 mm., and (*b*) 1·7 g., b. p. 170—180°/14 mm. As fraction (*a*) gave a nitroprusside reaction for thiol groups, it was dissolved in ether and extracted with aqueous sodium hydroxide. The ethereal solution now gave a sulphur-free product, b. p. 209°/741 mm., which proved to be *dimethylnonylamine* (Found: C, 77·1; H, 14·7. $C_{11}H_{25}N$ requires C, 77·7; H, 14·1%). The *methiodide* separated from water in filmy leaflets, m. p. 170° (Found: C, 45·9; H, 9·1. $C_{12}H_{28}NI$ requires C, 46·0; H, 9·0%). The thiol isolated from the sodium hydroxide extract by acidification in the presence of ether was benzylthiol (0·4 g.), b. p. 195—197°; the 2 : 4-dinitrophenyl thioether prepared from it had m. p. 128°; Bost, Turner, and Norton (*J. Amer. Chem. Soc.*, 1932, **54**, 1985) give m. p. 130° (Found: C, 54·2; H, 3·9. Calc.: C, 53·8; H, 3·7%).

Fraction (*b*) solidified and crystallised from methyl alcohol in bold plates, m. p. and mixed m. p. with dibenzyl sulphide 47°. The dibenzylsulphine-*p*-toluenesulphonylimine prepared from it had m. p. 191° (Mann and Pope, *J.*, 1922, **121**, 1053, give m. p. 193°).

Methylnonylamine.—(*a*) Nonyl bromide (20·7 g.) was converted into nonyl iodide (24·0 g.), b. p. 116°/15 mm. by Finkelstein's method. The iodide was mixed with methylamine (20 c.c.; 33% solution) in methyl alcohol and heated at 100° for 6 hours. The product was treated with aqueous sodium hydroxide, and the excess of methylamine and alcohol distilled off on the water-bath. The product extracted from the alkaline solution by ether was fractionally distilled, giving methylnonylamine (2·6 g.), b. p. 92—94°/15 mm., identified as its hydrochloride, m. p. 179—180° (see below), and *methyldinonylamine* (10·0 g.), b. p. 190—192°/15 mm. (Found: C, 80·5; H, 14·4. $C_{19}H_{41}N$ requires C, 80·6; H, 14·5%).

(*b*) *By Decker's method.* Nonylamine (9·0 g.), b. p. 85°/13 mm., was condensed with benzaldehyde (7 g.; 1·1 mols.) by heating on the water-bath for 1 hour. The *benzylidenenonylamine* was distilled under reduced pressure (yield, 13·6 g.), b. p. 179°/14 mm. (Found: C, 82·5; H, 11·2; N, 6·6. $C_{16}H_{25}N$ requires C, 83·1; H, 10·8; N, 6·3%). This was mixed with methyl iodide (8·4 g.; 1·1 mols.) and after 1 hour heated on the water-bath for 3 hours. The dark red, viscous oil was diluted with 90% ethyl alcohol (40 c.c.) and digested on the water-bath for 1 hour; the alcohol was then removed by distillation, the residue acidified, and the benzaldehyde removed by ether extraction. *Methylnonylamine* (6·6 g.), recovered from the acid solution, had b. p. 95°/14 mm. (Found: N, 9·1. $C_{10}H_{23}N$ requires N, 9·1%). The *hydrochloride* separated from acetone in needles or plates, m. p. 180—181° (Found: C, 61·6; H, 12·6. $C_{10}H_{23}N$,HCl requires C, 62·0; H, 12·5%).

Quininic Acid.—Thielepape's procedure (*Ber.*, 1939, **72**, 1432) was in the main followed, but it was found advan-

tageous when preparing α-ethoxalyl-*N*-methyl-*p*-methoxyacetanilide to dissolve the *N*-methyl-*p*-methoxyacetanilide (17·9 g.) in the ethyl oxalate (13·4 c.c.) and to add this slowly to a hot solution of sodium ethoxide (2·3 g. of sodium in 11·6 c.c. of absolute ethyl alcohol). Heating was continued for 2 hours, and the product (16·5 g.) isolated and purified as described by Thielepape.

Conversion of ethyl 2-chloroquininate into quininic acid as described by Thielepape was laborious and the yields were not satisfactory. The following process gave better results: Ethyl 2-chloroquininate (53 g.) was boiled vigorously with sodium hydroxide (9·0 g. in 1 l. of water) for 2 hours, the solution concentrated under reduced pressure to 350 c.c., sodium hydroxide (9·0 g.) and a palladium–strontium carbonate catalyst (2·0 g.) added, and the solution hydrogenated at 5 atms. for 45 minutes. The catalyst was collected and re-used for subsequent batches. Quininic acid was precipitated by addition of hydrochloric acid until the reaction of the solution was definitely acid to Congo-paper. The yield was almost quantitative.

Ethylhexylaminomethyl-6-methoxy-4-quinolylcarbinol.—Powdered 6-methoxy-4-quinolyl bromomethyl ketone hydrobromide (6·6 g.) (King and Work, *loc. cit.*) was added slowly to ethylhexylamine (7·1 g.) in acetone (10 c.c.). After 1 hour the mixture was warmed at 45° for 45 mins. and diluted with dry ether, and the ethylhexylamine hydrobromide collected (7·0 g.). The ethereal solution was washed with water, and the ether removed in a vacuum. A portion of the residual oil (2·5 g.) was dissolved in ethyl alcohol, concentrated hydrochloric acid added until the solution was acid to Congo-paper, and the product reduced, platinum oxide being used as catalyst (hydrogen consumed, 250 c.c.). *Ethylhexylaminomethyl-6-methoxy-4-quinolylcarbinol dipicrate*, isolated from the reduction mixture in 20% yield, had m. p. 170° and was soluble in hot ethyl alcohol (Found: C, 48·8; H, 4·5; N, 14·6. $C_{20}H_{30}O_2N_2,2C_6H_3O_7N_3$ requires C, 48·8; H, 4·6; N, 14·2%). Methyl-6-methoxy-4-quinolylcarbinol picrate was isolated as a by-product and its formation in quantity accounts for the low yield of the desired base.

Propylhexylaminomethyl-6-methoxy-4-quinolylcarbinol.—The product obtained from the appropriate bromomethyl ketone hydrobromide (7·1 g.) and propylhexylamine (8·5 g.) was reduced in the usual way. The resultant oil (5·8 g.) had to be fractionated by the method of differing basicities (cf. King and Ware, J., 1941, 331) before any crystalline derivatives could be obtained. The required *dipicrate*, m. p. 169°, was crystallised from acetone–ethyl alcohol; yield, 17% (Found: C, 49·8; H, 5·1. $C_{21}H_{32}O_2N_2,2C_6H_3O_7N_3$ requires C, 49·5; H, 4·8%).

Methylnonylaminomethyl-6-methoxy-4-quinolylcarbinol.—Condensation of methylnonylamine (4·0 g.) with 6-methoxy-4-quinolyl bromomethyl ketone hydrobromide (3·07 g.), reduction, and fractionation of the product gave an oil (1·06 g.), which was separated by fractional crystallisation into methylmethoxyquinolylcarbinol picrate and *methylnonylaminomethyl-6-methoxy-4-quinolylcarbinol dipicrate*, m. p. 151°, readily soluble in hot ethyl alcohol (Found: C, 50·9; H, 5·2; N, 13·4. $C_{32}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·0; H, 4·9; N, 13·7%).

Butylhexylaminomethyl-6-methoxy-4-quinolylcarbinol.—The condensation with butylhexylamine (9·4 g.) and subsequent reduction were carried out as described for the lower homologue. The *dipicrate* (0·7 g.), m. p. 158—159°, was sparingly soluble in ethyl alcohol (Found: C, 50·8; H, 5·2; N, 14·5. $C_{22}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·0; H, 4·9; N, 13·7%).

2′ : 2′ : 6′-Trimethylpiperidinomethyl-6-methoxy-4-quinolylcarbinol.—2 : 2 : 6-Trimethylpiperidine (6·0 g.) was condensed with the bromoketone hydrobromide (5·73 g.), and the product reduced (hydrogen consumed, 340 c.c.). From the ether-soluble fraction of the product a crystalline hydrochloride (0·7 g.), m. p. 214—218° (decomp.), was isolated by fractional crystallisation from ethyl alcohol. Although apparently homogeneous, this hydrochloride did not give satisfactory analytical figures. It was converted into the *dipicrate*, m.p. 214°, which was crystallised repeatedly from acetone containing 5% of free picric acid (Found: C, 49·4; H, 3·8. $C_{20}H_{28}O_2N_2,2C_6H_3O_7N_3$ requires C, 48·9; H, 4·3%).

Attempts to obtain morpholinomethyl-6-methoxy-4-quinolylcarbinol were unsuccessful, reduction always leading to formation of methyl-6-methoxy-4-quinolylcarbinol.

We are grateful to Miss Ann Bishop, D.Sc., working in the laboratory of Prof. Keilin, F.R.S., at the Molteno Institute, Cambridge, for the biological results. To Mr. E. V. Wright and Mr. N. Schunmann we are indebted for technical assistance.

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73. *The Comparative Reactivity of the Carbonyl Groups in the Thionaphthenquinones. Part I. The Constitution of Certain Thioindigoid Dyes.*

By John Harley-Mason and Frederick G. Mann.

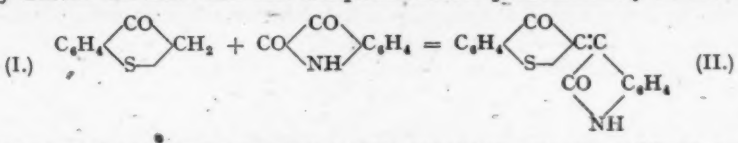
In view of the scanty and conflicting evidence hitherto available, an investigation has been made of the factors determining the type of condensation of the thioindoxyls with the thionaphthenquinones, *i.e.*, whether the methylene group of the former reacted with the α-carbonyl group of the latter to give a thioindigo or with the β-carbonyl group to give a thioindirubin. For this purpose, thioindoxyl and six substituted thioindoxyls have been condensed with the corresponding thionaphthenquinones, and the product in each case compared with that obtained by the condensation of the thioindoxyl with the corresponding α-anil, where α-condensation must necessarily have occurred. The results show that the condensation in most cases is determined solely by the position of substituents in the quinone molecule and is unaffected by those in the thioindoxyl molecule: thionaphthenquinone and 5- or 6-substituted thionaphthenquinones always give β-condensation, 4-substituted quinones always give α-condensation, and 7-substituted quinones may give α- or β-condensation: only with the last quinones, therefore, is the type of condensation affected by the thioindoxyl employed.

Indoxyl and oxindole, however, always give β- and α-condensation respectively with all the thionaphthenquinones investigated, the effect of these two compounds being thus to suppress completely the influence of substituents in the quinone molecule. The significance of these results is discussed.

It is known that compounds containing reactive methylene groups, such as indoxyl and thioindoxyl,* always condense with the 3- or β-carbonyl group of the isatin molecule: the reaction with thioindoxyl (I)

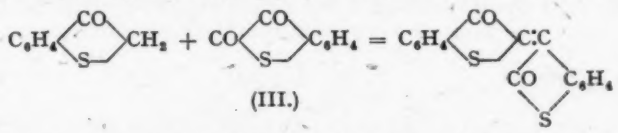
* This compound is correctly named 3-hydroxythionaphthen, but since in all the reactions cited in this paper it is reacting in the keto-form, it should systematically be termed 3-keto-2 : 3-dihydrothionaphthen. For brevity, however, and in accordance with common practice, the term thioindoxyl has been used throughout.

therefore gives the 2 : 3′-derivative (II). The non-reactivity of the 2- or α-carbonyl group of the isatin molecule is probably due to the fact that this compound reacts predominantly in the enol or lactim form.



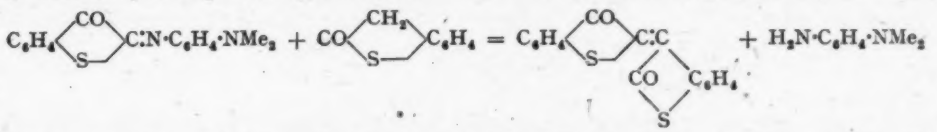
(I.) (II.)

In similar condensations with thionaphthenquinone (III), which cannot show this type of tautomerism, the scanty evidence available showed that the β-carbonyl group did not possess this markedly greater reactivity over the α-carbonyl group. Indoxyl and thioindoxyl, *e.g.*, condense with the β-carbonyl group of thionaphthenquinone (Friedländer, *Monatsh.* 1908, **29**, 373, 375): the structure of the dye thus obtained from indoxyl

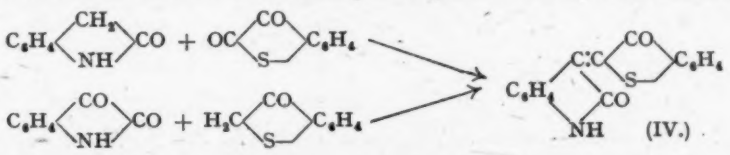


(III.)

was proved by its alkaline fission products (Friedländer *et al.*, *Ber.*, 1910, **43**, 1971; 1911, **44**, 3107); that of the dye from thioindoxyl was proved by the fact that the same dye could be prepared by the condensation of

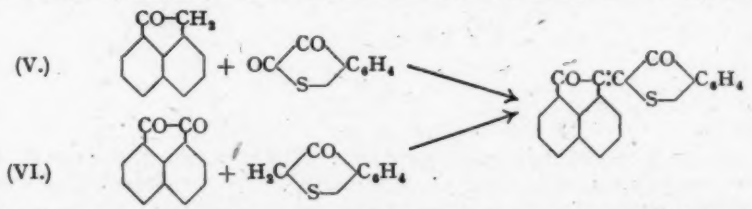


the *p*-dimethylaminoanil of thioindoxyl with thio-oxindole (Marschalk, *J. pr. Chem.*, 1913, **88**, 227). On the other hand, there have been several examples cited (mainly in patent literature) in which similar reactions involve the α-carbonyl group of the quinone molecule. For example, thioindigo scarlet (IV) is obtained by the condensation of oxindole with thionaphthenquinone and by the condensation of isatin with



(IV.)

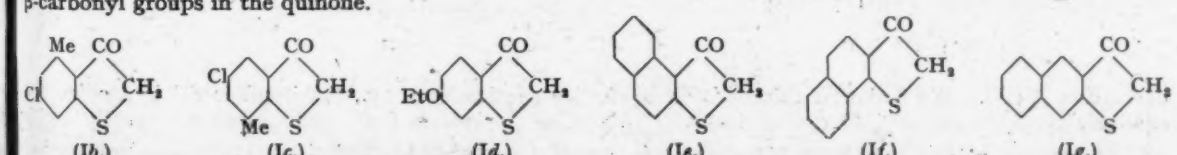
thioindoxyl (E.P. 214,864). Similarly, it has been claimed that identical products are obtained by the condensation of acenaphthenone (V) with thionaphthenquinone and of acenaphthenquinone (VI) with thioindoxyl (D.R.-P. 205,377, 226,244): this would indicate that here again the α-carbonyl group of the quinone



(V.) (VI.)

molecule has undergone condensation. Several other similar examples could be given (*e.g.*, E.P. 214,864, 222,094, 232,230).

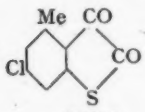
Although the condensation of substituted thioindoxyl and similar compounds with substituted thionaphthenequinones is largely used in dye manufacture, the true constitution of the dye—dependent upon whether the α-carbonyl group of the quinone has condensed to give an indigo or the β-carbonyl group condensed to give an indirubin—has usually been either assumed without evidence or else ignored. The object of the present investigation was therefore to carry out a number of such condensations, to determine the structure of the products, and thus if possible to determine also the factors which control the reactivity of the α- and β-carbonyl groups in the quinone.

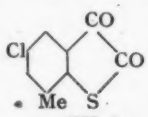


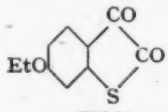
(Ib.) (Ic.) (Id.) (Ie.) (If.) (Ig.)

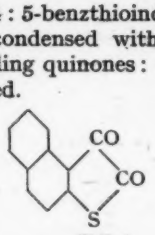
For this purpose, the following thioindoxyls were used, these compounds being chosen because they could be readily prepared from technical materials: thioindoxyl (I); 6-chloro-4-methylthioindoxyl (Ib); 5-chloro-

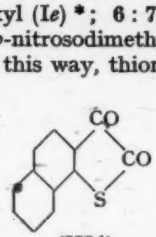
7-methylthioindoxyl (I*c*); 6-ethoxythioindoxyl (I*d*); 4 : 5-benzthioindoxyl (I*e*) *; 6 : 7-benzthioindoxyl (I*f*); 5 : 6-benzthioindoxyl (I*g*). These compounds were condensed with *p*-nitrosodimethylaniline to give the anils, and the latter on hydrolysis gave the corresponding quinones: in this way, thionaphthenquinone (III) and the substituted quinones (III*b*—III*g*) were prepared.

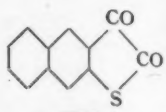

(III*b*.)


(III*c*.)

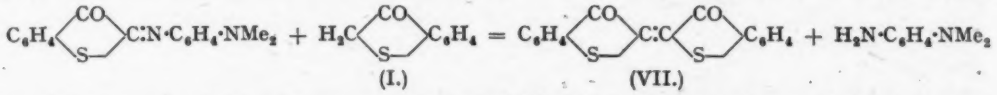

(III*d*.)


(III*e*.)


(III*f*.)


(III*g*.)

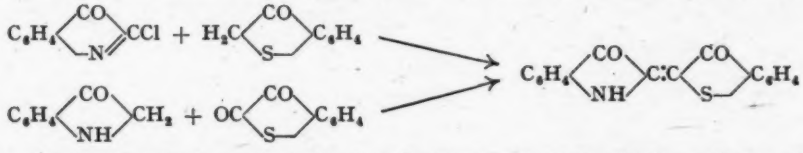
The various thioindoxyls were then condensed with each of the quinones, and the product in each case compared with that obtained by the interaction of the thioindoxyl with an anil. In the latter reaction, condensation to a dye must occur at the 2- or α-carbon atom, and such compounds were therefore used as reference


(I.) (VII.)

compounds of known structure. If the product of condensation of the thioindoxyl and the quinone were identical with the product from the anil, then clearly the α- or 2-carbonyl group of the quinone had undergone condensation: if the compounds were different, then the β- or 3-carbonyl group of the quinone had reacted.

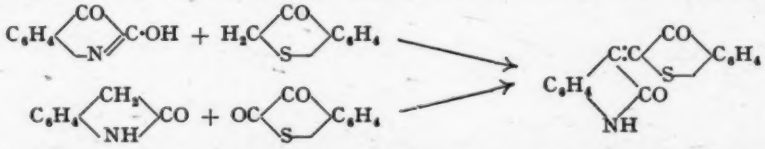
In certain cases, the reference compound having the 2 : 2′-structure could be made more expeditiously than through the anil intermediate. Thus symmetric derivatives such as (VII) could also be prepared by direct oxidation of the thioindoxyl (I) with alkaline ferricyanide.

In addition to the use of the thioindoxyls (I—I*g*), indoxyl and oxindole were also condensed with the quinones (III—III*g*), in order to determine whether the presence and position of the nitrogen atom in place of the sulphur would markedly affect the type of condensation obtained. For the indoxyl condensation, reference compounds of known structure were prepared by the condensation of isatin chloride with the



required thioindoxyl: the product must clearly be identical with that which would be obtained if indoxyl condensed with the α-carbonyl group of thionaphthenquinone.

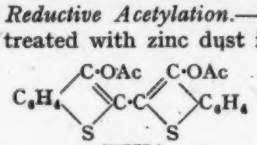
For the oxindole condensation, reference compounds were prepared by the condensation of isatin and thioindoxyl, whereby a product was obtained identical with that which would result from the condensation

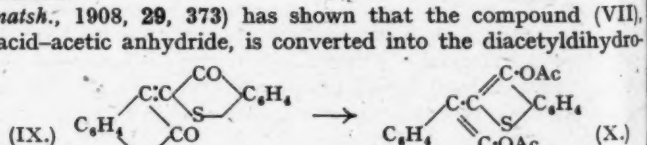


of oxindole with the α-carbonyl group of thionaphthenquinone. The structure of these reference compounds was further confirmed by the preparation of identical compounds by the condensation of oxindole with the anils obtained from the thioindoxyls.

In all the cases examined, therefore, a pair of compounds, one being a reference compound of known structure, was obtained: these compounds were usually deeply coloured, of high or indefinite m. p., and of very low solubility in most organic solvents. The means adopted to decide whether the members of each pair were identical or different must now be discussed.

1. *Reductive Acetylation.*—Friedländer (*Monatsh.*, 1908, **29**, 373) has shown that the compound (VII), when treated with zinc dust in boiling acetic acid–acetic anhydride, is converted into the diacetyldihydro-


(VIII.)

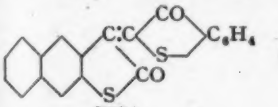

(IX.) (X.)

derivative (VIII). We find that this reaction is of wide application; *e.g.*, the isomeric thioindirubin (IX) similarly gives the diacetyl-dihydro-derivative (X). These derivatives from both classes are usually highly

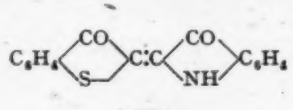
* Compounds of this type have frequently been named "naphthathioindoxyl" or "naphtha-3-hydroxythionaphthene": these names are clearly incorrect, as they imply the existence of three fused benzene rings. The term "4 : 5-benzthioindoxyl" has been adopted for greater accuracy and particularly to emphasise the position of the substituents in the main benzene ring.

crystalline, sparingly soluble compounds of sharp m. p., and this reductive method has proved the most valuable of the chemical methods available for the characterisation and identification of the original dye. The diacetyl-dihydro-derivatives of the thioindirubins were always more soluble and had lower m. p.'s than the corresponding thioindigo derivatives.

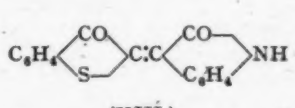
This reductive method cannot be applied, however, to all types of compound prepared in this investigation: diacetyl-dihydro-derivatives were not obtained from thioindirubins of type (XI) containing one linear naphthalene residue, or from the mixed sulphur-nitrogen compounds of types (XII), (XIII), and (XIV), which appeared to undergo fission at the double bond.



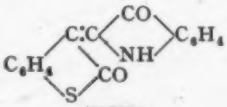
(XI.)



(XII.)



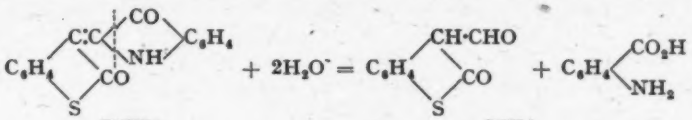
(XIII.)



(XIV.)

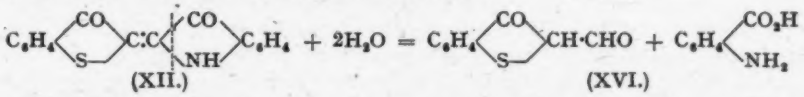
2. *X-Ray Analysis.*—The dyes, after recrystallisation from boiling nitrobenzene or acetic anhydride, lend themselves readily to *X*-ray photography by the "powder" method, which therefore affords an excellent method of comparing the identities of each pair of substances. This work has been kindly undertaken by Dr. W. H. Taylor and Dr. A. Hargreaves of the Physics Department of the Manchester College of Technology. Their results concerning the identity of the thioindoxyl condensation products agree with our results, apart from two pairs of substances (see Tables VI and VII) where our diacetyl-dihydro-derivatives had m. p.'s too high for reliable comparison and where therefore the *X*-ray evidence alone was available. The *X*-ray work has thus afforded a valuable and entirely independent confirmation of our chemical methods of comparison.

3. *Alkali Fission.*—Friedländer (*loc. cit.*) has applied this reaction to the unsubstituted thio-indigos and -indirubins. We find, however, that substituted derivatives of each class are very resistant to alkali, and this reaction has been applied, therefore, only to compounds of type (XII), (XIII), and (XIV), to which reductive acetylation cannot be applied. Thus compounds of type (XIV) are readily decomposed by alkali to



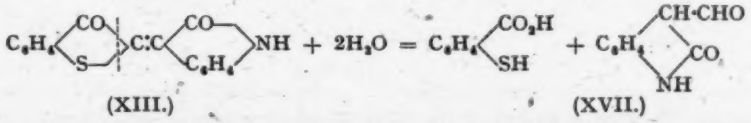
(XIV.) (XV.)

give anthranilic acid and the thio-oxindole-3-aldehyde (XV). Compounds of type (XII) break down less readily, giving anthranilic acid and thioindoxyl-2-aldehyde (XVI). These aldehydes form well-crystallised phenylhydrazones, and a number have thus been characterised.



(XII.) (XVI.)

Compounds of type (XIII) decompose still less readily with alkali, giving a thiosalicylic acid and oxindole-3-aldehyde (XVII). Since, however, the isolation of the substituted thiosalicylic acids proved difficult,



(XIII.) (XVII.)

alkali-splitting of compounds of type (XIII) has not been extensively employed, and the comparison of the oxindole condensation products with their reference compounds has therefore been made throughout by *X*-ray analysis.

4. *Dyeing Tests.*—The members of each pair of compounds could be compared by carrying out dyeing tests on cotton under strictly controlled and parallel conditions. This method proved satisfactory for those compounds which underwent vatting without decomposition. Some compounds proved too unstable: *e.g.*, thioindirubins having substituents in only one benzene ring were almost completely broken down during vatting and were thus almost useless as dyes, whereas similar compounds having substituents in both rings were stable to vatting and formed moderately good dyes, being usually weaker and paler than the corresponding thioindigos.

5. *Colours of Sulphuric Acid Solutions.*—All the dyes prepared in this work, when dissolved in cold concentrated sulphuric acid, gave intense colours entirely different from those of the parent dyes. Since, however, the colour of these solutions was much affected by traces of impurities, this test was employed only when markedly different colours produced by two compounds in solution proved their non-identity. The use of this test was therefore solely confirmatory to certain results obtained by previous tests.

The detailed data provided by these five tests are discussed later. The final conclusion so obtained for the identity of each compound prepared by the condensation of the thioindoxyl (or other $>CH_2$ compound)

with the thionaphthenquinone is given in Table I, and may conveniently be discussed here. Not every member has been prepared, as this would have involved the preparation and critical examination of over 120 compounds: sufficient have been made to show beyond reasonable doubt how each quinone condenses with the various cyclic methylene compounds employed. It should be emphasised that no example of a mixture of α- and β-condensation products arising in one reaction was found, in spite of a very close scrutiny which, we consider, would have detected the second isomeric form had it constituted more than 5% of the product: each reaction therefore appeared to give solely α- or β-products.

If the condensation products of the quinones with the various thioindoxyls alone are first considered, the results in Table I indicate clearly: (i) Thionaphthenquinone and all derivatives having substituents solely in the 5- or the 6-position or both (*i.e.*, III, III*d*, III*g*) condense only with the β-carbonyl group, irrespective of the nature of the thioindoxyl employed. [In compounds such as (III*g*) the second benzene ring fused on to the main ring is regarded as two substituent groups.]

TABLE I.

	(III.)	(III*b*.)	(III*c*.)	(III*d*.)	(III*e*.)	(III*f*.)	(III*g*.)
(I.)	β	α	α		α	α	β
(I*b*.)	β	α		β	α		
(I*c*.)			α	β	α	α	β
(I*d*.)	β	α	α	β	α	β	β
(I*e*.)	β	α	α		α	β	β
(I*f*.)	β	α	β	β	α	α	β
(I*g*.)	β	α	α	β	α	α	β
Indoxyl ...	β	β	β	β	β	β	β
Oxindole	α	α	α	α	α	α	α

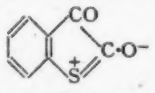
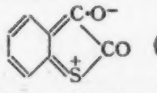
(ii) Thioquinones having a substituent in the 4-position (III*b*, III*e*) condense only with the α-carbonyl group, and this behaviour is apparently unaffected by other substituents in the benzene ring.

(iii) Thioquinones having a substituent in the 7-position (III*c*, III*f*) condense with the α- or the β-carbonyl group, according to the thioindoxyl employed: the 7-substituent appears thus to have no decisive influence. In view of this fact it is particularly noteworthy that even in these reactions, a mixture of α- and β-products from one pair of reactants was never detected.

It is remarkable, therefore, that, whereas the nature of the condensation product in the examples (i) and (ii) above appears to be determined solely by the substituents in the thionaphthenquinone molecule, the completely reverse effect is found when indoxyl and oxindole condense with these quinones. Here it will be seen (Table I) that indoxyl gives solely β-condensation and oxindole solely α-condensation irrespective of the thioquinone employed, the effect of the nitrogenous molecule in each case being sufficiently strong to over-ride any influence exerted by the quinone molecule itself.

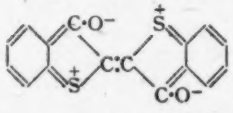
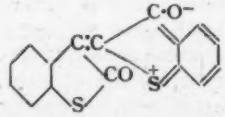
These results correct certain previous inaccuracies. Thus Dutta (*Ber.*, 1934, **67**, 1324) has indicated that the thioindoxyl (I*g*) condenses with the β-carbonyl group of both quinones (III*e*) and (III*f*): it is now shown that both these quinones give α-condensation with (I*g*).

It is impossible at present to explain with any degree of certainty the theoretical basis of the results summarised in Table I: these results will have to be extended to many other substituted thioindoxyls and quinones before the experimental data are sufficiently extensive to warrant reliable generalisations. Certain theoretical points should, however, be noted. It has already been pointed out that the exclusive β-condensation of isatin can be explained on its tautomeric nature, but that such tautomerism is impossible with thionaphthenquinone. Nevertheless the latter must be a resonance hybrid between the conventional form (III) and the polar structures (XVIII*a*) and (XVIII*b*). It is possible that of these polar structures the form

(XVIII*a*.)   (XVIII*b*.)

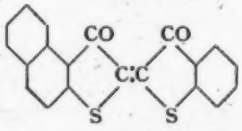
(XVIII*a*), in which the poles are nearest together, will predominate, and this may be the reason for the greater reactivity of the β-carbonyl group in the unsubstituted thionaphthenquinone. The introduction of substituents into the benzene ring (and hence of further dipoles) will change the nature of the resonance hybrid relative to the parent forms, and hence change also the relative reactivity of the two carbonyl groups. The correlation of the nature and position of such substituents with proportionality of the resonance hybrid cannot yet be made.

A second factor may arise. It has been shown by Ries and Schneider (*Z. Krist.*, 1928, **68**, 543) by *X*-ray analysis that the indigo molecule has a centre of symmetry: this is to be expected if the molecule exists as a resonance hybrid between the normal form and Kuhn's polar form (*Naturwiss.*, 1932, **20**, 618), in which the molecule would be most stable when opposite poles are at a minimum distance apart. Similar considerations apply to thioindigo; this undoubtedly exists as a hybrid between the normal form (VII) and the polar structure (VII*a*), which therefore probably exists also as the more stable *trans*-form, although there is at

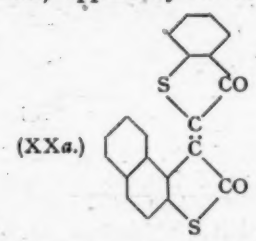
(VII*a*.)   (IX*a*.)

present no experimental evidence available on this point. Similarly the isomeric thioindirubin may exist as a hybrid between the form (IX) and the polar form (IX*a*), although here a symmetric (and presumably more

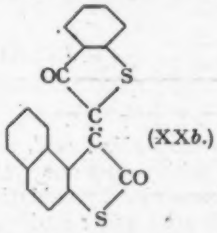
stable) polar structure cannot be achieved. It follows, however, that the existence of resonance in both thio-indigo and thio-indirubin will alter the normal inter-atomic distances and atomic sizes, the true values of which are therefore unknown. This is unfortunate, since lack of this knowledge makes it impossible to say decisively whether in certain cases the results summarised in Table I may not be due partly to steric hindrance. Thus it is noteworthy that the quinone (III*e*) always condenses with thioindoxyls by its α-carbonyl group, *i.e.*, with thioindoxyl itself the compound (XIX) is readily formed, whereas the *cis*- or *trans*-forms of the β-product (XX*a* and XX*b*) apparently do not exist. There is a possibility of steric



(XIX.)



(XX*a*.)



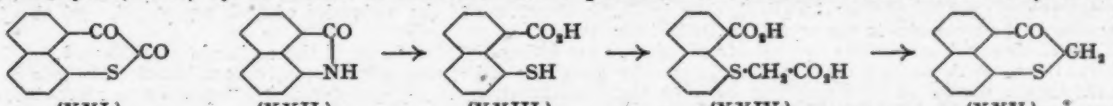
(XX*b*.)

hindrance in both the latter compounds (greater in XX*b* than XX*a*), and this factor may be partly responsible for the fact that substituents in the 4-position cause condensation solely at the α-carbonyl group, whereas those in the 7-position (where steric hindrance is impossible) are without decisive effect.

It must be admitted, however, that neither of the above factors (the hybrid structure of the quinone or the steric factor in the condensation product) affords a reasonable explanation why indoxyl itself condenses solely with the β-carbonyl group, and oxindole solely with the α-carbonyl group, of all the thioquinones studied.

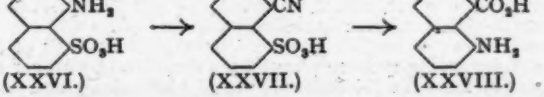
We are now engaged in the preparation of thioindoxyls and thionaphthenquinones having substituents solely in the 4- and in the 7-positions in order to widen the scope of our experimental data regarding these condensations.

Apart from the main investigation described above, certain other results should be noted. The condensation of the various thioindoxyls (I—I*g*) with 1-*peri*-naphthathiopyran-2 : 3-dione (XXI) would be of great interest, as the latter compound, although isomeric with the quinones (III*e*, III*f*, and III*g*), differs from them in having a 6-membered quinone ring. The corresponding thiopyran-3-one (XXV), corresponding to the thioindoxyls, has been synthesised by Friedländer and Woroshow (*Annalen*, 1912, **388**, 1) by converting naphthastyril (XXII) by the action of nitrous acid and potassium xanthate into the thiol-carboxylic acid



(XXI.) (XXII.) (XXIII.) (XXIV.) (XXV.)

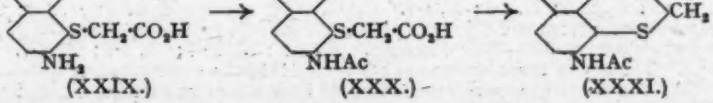
(XXIII), condensing the latter with chloroacetic acid to the dicarboxylic acid (XXIV), and cyclising the latter with loss of carbon dioxide to give the required derivative (XXV). We have repeated this synthesis with great difficulty : the purification of the acid (XXIV) proved laborious and wasteful, and the yield of the final product (XXV) was very low. Although the investigation of (XXV) was in consequence abandoned, the various methods for the preparation of naphthastyril (XXII) have been critically examined. The earliest method, consisting in the reduction of 8-nitro-1-naphthoic acid, was not examined in detail, owing to the difficulty of obtaining this acid free from isomerides. The Hofmann degradation of 1 : 8-naphthalimide (Ullmann and Cassirer, *Ber.*, 1910, **43**, 440; Pisovschi, *Bull. Soc. chim.*, 1911, **9**, 87) gave very low yields. The best method consisted in the conversion of 1-naphthylamine-8-sulphonic acid (XXVI) by Sandmeyer's reaction (D.R.P., 444,325) into the 1-cyano-acid (XXVII), which on potash fusion gave the 8-amino-1-



(XXVI.) (XXVII.) (XXVIII.)

naphthoic acid (XXVIII) (E.P. 276,126) : the yield of the naphthastyril (XXII) thus obtained from the *peri*-acid (XXVI) was 60%.

Certain substituted derivatives of (XXV) were also investigated: The conversion of sodium 2-naphthyl-

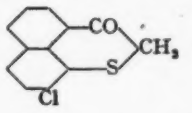


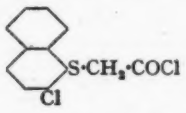
(XXIX.) (XXX.) (XXXI.)

amine-1-thioglycollate (XXIX) in aqueous solution by acetic anhydride into the acetamido-compound (XXX) (D.R.-P. 408,021) has been improved : this reaction must be performed in aqueous solution, since treatment

of the sodium salt with acetic anhydride causes rapid cyclisation to the very stable unacetylated lactam, the free acid being apparently incapable of existence. The isolation of 9-acetamido-1-*peri*-naphthathiopyran-3-one (XXXI), after cyclisation of the 2-acetamido-compound (XXX) with chlorosulphonic acid (D.R.-P. 414,084), failed, however, in spite of wide variation in the conditions employed: in these circumstances the $>CH_2$ group in (XXXI) always underwent oxidation, with consequent formation of the thioindigoid dye.

9-Chloro-1-*peri*-naphthathiopyran-3-one (XXXII) is cited in D.R.-P. 362,551, but its preparation is not mentioned. 2-Naphthylamine-1-thioglycollic acid (XXIX) was therefore converted by Sandmeyer's reaction

(XXXII.) 



(XXXIII.)

into the 2-*chloro-acid*, and the latter converted into the acid chloride (XXXIII). Cyclisation of the latter to the thiopyran-3-one (XXXII) by the action of aluminium chloride in chlorobenzene was, however, always accompanied by oxidation, with the consequent formation of the corresponding thioindigo. Chlorosulphonic acid, used under various conditions, either left the chloride (XXXIII) unchanged or gave small yields of the thioindigo. In these circumstances, work on the *peri*-derivatives has been temporarily abandoned.

Although the condensation of acenaphthenone with various substituted thioquinones to give good dyes has been claimed (D.R.-P. 463,001, E.P. 189,782, 214,864, 236,332), we find that acenaphthenone condensed with the quinones (III—III*g*) to give brown products that were obviously mixtures and almost useless as dyes. In particular, the claim to prepare 2-thionaphthene-acenaphthene-indigo by condensation with thionaphthenequinone itself (see p. 405) could not be confirmed. Since, moreover, the preparation of pure acenaphthenone is a long and wasteful process, the products of this type of condensation were not further investigated.

Experimental.

Several of the following compounds, whose preparation has been claimed in patent literature without proof of identity, are now recorded as new.

Solvents used for recrystallisation are named in parenthesis after the compounds concerned.

With regard to the *X*-ray results, Dr. Taylor and Dr. Hargreaves report: "Pairs of dyes have been examined in an attempt to decide whether the two individuals of each pair are identical. For this purpose, powder photographs have been taken with (filtered) Kα radiation in a camera of diameter 19 cm.

"Using carefully purified samples of the dyes, the conclusions to be drawn from a comparison of the powder photographs of two compounds are:

(1) If the photographs are identical, then both the structures of the molecules of each compound, and also the packing of the molecules in the crystal, must be identical.

(2) If the photographs are completely different, then either the structures of the molecule are different, or (less likely) the mode of packing is different although the structures of the molecules themselves are identical. Since there is no simple means of distinguishing between these alternatives, *X*-ray powder photographs do not provide an unequivocal solution to the problem."

In the following Tables the abbreviations "Id." and "Non-id." indicate results obtained in (1) and (2) respectively.

Preparation of Intermediates.—Thioindoxyls. All the thioindoxyls except (I*f*) and (I*g*) were obtained from technical sources and purified. The thioindoxyl (I*f*) was obtained from β-naphthylamine by the Herz sulphur chloride method (D.R.-P. 367,344). The thioindoxyl (I*g*) was prepared as follows: Sodium hydroxide (22 g.), 2-amino-3-naphthoic acid (93 g.), and sodium nitrite (36 g.) were dissolved in turn in water (1 l.), and the solution run slowly into a well-stirred mixture of concentrated hydrochloric acid (170 c.c.) and ice (300 g.). The diazo-solution was neutralised with sodium carbonate (Congo-red) and run into a solution of sodium disulphide, prepared from sodium sulphide nonahydrate (60 g.) and sulphur (8 g.) in water (150 c.c.), with vigorous stirring at 25°. The solution was slowly heated to 80°, and sodium hydrosulphite (30 g., an excess) added, the solution being kept alkaline to phenolphthalein. To the solution of sodium 2-thiol-3-naphthoate thus obtained was added a solution of chloroacetic acid (80 g.) and sodium hydroxide (40 g.) in water (300 c.c.); the mixture after filtration was maintained at 90° for 1 hour. After cooling, addition of hydrochloric acid precipitated 3-*carboxynaphthyl*-2-*thioglycollic acid*, which was isolated in white crystals (alcohol–benzene), m. p. 175—176° (Found: C, 57·6; H, 3·7. $C_{13}H_{10}O_4S$ requires C, 57·8; H, 3·6%). The crude acid from the precipitation was stirred into a solution of sodium hydroxide (200 g.) in water (50 c.c.) at 140°; after 1 hour at 130—140°, the melt was dissolved in hot water, and the thioindoxyl (I*g*) precipitated from the filtered solution with hydrochloric acid at 90° as a greenish-yellow microcrystalline powder (87 g.).

Anils and thionaphthenquinones. The preparation of the *p*-dimethylamino-anils of the thioindoxyls (I—I*e*) and of (I*g*) and their hydrolysis to the corresponding quinones have been described by Mayer *et al.* (*Annalen*, 1931, **488**, 259). The preparation of the *p*-hydroxy-anils from the thioindoxyls was also examined, and only those from (I), (I*d*), and (I*g*) could be satisfactorily prepared. To an alkaline solution of thioindoxyl (30 g.; sodium hydroxide, 20 g.; water, 300 c.c.) at 50°, a solution of *p*-nitrosophenol (26 g.) and sodium hydroxide (20 g.) in water (300 c.c.) was added. After 1 hour, sodium chloride (100 g.) was added, and the sodium salt collected. A portion, treated with dilute acetic acid, gave thionaphthenquinone-2-*p*-hydroxyanil (*n*-butyl alcohol), m. p. 251—252°; Mayer (*loc. cit.*) obtained it as a by-product when preparing the *p*-dimethylamino-anil. 6-*Ethoxythionaphthenquinone*-2-p-*hydroxyanil*, similarly prepared from the thioindoxyl (I*c*) (30 g.) and *p*-nitrosophenol (21 g.), formed brownish-yellow needles (glycol monoethyl ether), m. p. 237—239° (Found: C, 67·6; H, 4·8; N, 4·7. $C_{16}H_{13}O_3NS$ requires C, 67·8; H, 4·6; N, 4·9%). 6:7-*Benzthionaphthenquinone*-2-p-*hydroxyanil*, from the thioindoxyl (I*f*) (30 g.) and *p*-nitrosophenol (22 g.), formed brownish-red crystals (glycol monoethyl ether), m. p. 280—282° (decomp.) (Found: C, 70·7; H, 3·9; N, 4·7. $C_{17}H_{11}O_3NS$ requires C, 70·8; H, 3·6; N, 4·6%). The above three anils were converted into the corresponding quinones by hydrolysis with hot hydrochloric acid (15%); the crude quinones were dissolved in hot sodium carbonate solution, which was acidified after filtration to precipitate the pure material.

Oxindole was prepared by the cyclisation of α-chloroacetanilide in the presence of aluminium chloride, thio-oxindole in low yield by Marschalk's method (*loc. cit.*), isatin in good yield by the method described in D.R.-P. 229,815, isatin

chloride by Baeyer's method (*Ber.*, 1879, **12**, 456; it remained unchanged for many months in a well-closed bottle), and acenaphthenone by Graebe's method (*Annalen*, 1896, **290**, 198).

Preparation of Dyes.—General conditions are given below; an excess (1·2 mols.) of the second reactant was used throughout to ensure the absence of the slightly soluble first reactant in the product.

(1) *Condensation of thionaphthenquinones with thioindoxyls.* A mixture of the quinone (1—2 g.), the thioindoxyl (1·2 mols.), glacial acetic acid (30 c.c.), and zinc chloride (*ca.* 0·2 g.) was refluxed for 2 hours. A shorter period would have sufficed in some cases; *e.g.*, 30 mins. for (III*e*) and (III*f*). The zinc chloride could sometimes be replaced by concentrated hydrochloric acid (2 drops), but longer boiling was then required. After cooling, the dye was collected and washed with alcohol and water. Yields, usually about 70%. For dyeing tests, unrecrystallised material was used, as it was much more readily dispersed than crystallised material. For analysis and *X*-ray examination, the dye was recrystallised from boiling nitrobenzene, washed with benzene and alcohol, and dried at 130°/12 mm.

(2) *Condensation of anils with thioindoxyls, indoxyl, oxindole, and acenaphthenone.* This was performed exactly as in (1), except that hydrochloric acid (1 drop) was used in place of zinc chloride [the latter combines with the *p*-dimethylamino-anils to give slightly soluble double salts (green iridescent needles) which do not undergo further reaction]. Yields, 75—95%.

(3) *Condensation of thionaphthenquinones with indoxyl and with oxindole.* That with indoxyl was carried out precisely as in (2) and proceeded readily; yields, almost quantitative. That with oxindole proceeded least readily of all, and was carried out in acetic anhydride with zinc chloride, the conditions being otherwise as in (1); yields about 70%.

(4) *Condensation of isatin with thioindoxyls.* This was carried out as in (2) and was generally complete after 30 mins.' boiling; yields, almost quantitative.

(5) *Condensation of isatin chloride with thioindoxyls.* This proceeded in acetic acid without the use of a condensing agent and was complete after 5 mins.' boiling; yields, almost quantitative.

(6) *Condensation of thionaphthenquinones with acenaphthenone.* This was attempted in acetic acid and in acetic anhydride, with and without zinc chloride. There was obtained only a low yield of brownish-black powder which could not be purified.

Preparation of Diacetyl-dihydro-derivatives (cf. Friedländer, *loc. cit.*).—Zinc dust was added to a boiling mixture of the dye (0·5 g.), acetic acid (5 c.c.), and acetic anhydride (5 c.c.). After 0·25—2 hours the colourless solution was filtered hot. The diacetyl-dihydro-compound (contaminated with zinc acetate), which crystallised on cooling, was dissolved in hot acetic anhydride and poured into water; the precipitated acetyl compound was recrystallised from acetic acid or acetic anhydride.

The acetyl derivatives of some of the simpler thioindirubins were moderately soluble in the above acetylating mixture, which therefore had to be slightly diluted with water to ensure initial separation of the derivative.

Alkali Fission of 2- and 3-Thionaphthen-2′-indole-indigos (XII *and* XIV) (cf. Friedländer, *loc. cit.*).—A mixture of the finely powdered dye (0·5 g.), 20% aqueous potassium hydroxide (7 c.c.), and alcohol (0·5 c.c.) was boiled until the solution became green and a grey precipitate of the aldehyde-potassium salt separated. After cooling, the precipitate was collected and dissolved in hot water; the solution was filtered and acidified with acetic acid. The precipitated aldehyde was recrystallised from dilute alcohol or converted into the phenylhydrazone.

Dyeing Tests.—A paste, prepared by grinding together the dye (0·1 g.), water (5 c.c.), and a few drops of Turkey red oil, was diluted with water (20 c.c.) and 10% aqueous solution hydroxide (2 c.c.), sodium hydrosulphite (0·5 g.) added, and the mixture heated in a stoppered flask at 70° until the dye had dissolved, a vatting assistant (*e.g.*, anthraquinone) being added if necessary. The vat was diluted with water to 200 c.c., 10% sodium hydroxide solution (4 c.c.) and sodium hydrosulphite (1 g.) added, and then a standard piece of the cotton fabric (2 g.). After the mixture had been kept at 70° for 30 minutes, the fabric was removed, wrung out, and suspended in the air for 5 minutes. It was then boiled for 30 minutes with 1% soap solution, washed thoroughly, dried, and ironed.

In some cases, a pair of compounds, proved by other means to be identical, gave slightly different tints on dyeing: this was probably due to faint traces of impurities in the quinone condensation products.

The thioindirubins often gave difficulty in dyeing (p. 407).

Tables II—VIII give the detailed evidence upon which the final conclusions stated in Table I have been based.

TABLE II.

Condensation of (A) *Thionaphthenquinone* (III), *and* (B) *its Anil, with the Thioindoxyls.*

Thioindoxyl.		*Diacetyl-dihydro-derivatives and m. p.*	*X-Ray data.*	*Dyeing Tests.*	*Condensation.*
Thioindoxyl (I)	A	Colourless needles, 148—149°		Very weak red	β
	B	Colourless needles, 248°		Bluish-red	
6-Chloro-4-methyl- (I*b*)	A	White plates, 144—145°		Pinkish-red	β
	B	White needles, 182—183°		Bright-red	
6-Ethoxy- (I*d*)	A	Colourless crystals, 131—133°		Weak orange	β
	B	Pink leaflets, 162—165°		Bright orange-red	
4 : 5-Benz- (I*e*)	A	Pale brown plates, 162—163°	Non-id.	Very weak brown	β
	B	Pale brown needles, 214—217°	,,	Bordeaux-red	
6 : 7-Benz- (I*f*)	A	Pale brown plates, 178—179°			β
	B	Colourless needles, 254—256°			
5 : 6-Benz- (I*g*)	A	Not formed (p. 407)	Non-id.	Very pale blue	β
	B	Pale green plates, 254—256°	,,	Blue	

6-*Chloro-4-methylthioindirubin* (Found: S, 18·9. $C_{17}H_9O_2ClS_2$ requires S, 18·7%); *diacetyl-dihydro*-derivative (Found: C, 59·0; H, 2·7. $C_{21}H_{13}O_4ClS_2$ requires C, 59·3; H, 2·6%); 6-*chloro-4-methylthioindigo* (Found: S, 18·9%) (U.S.P. 1,709,982); *diacetyl-dihydro*-derivative (Found: C, 59·0; H, 2·9%). 6-*Ethoxythioindirubin* (Found: S, 18·9. $C_{19}H_{15}O_3S_2$ requires S, 18·8%); *diacetyl-dihydro*-derivative (Found: C, 61·7; H, 4·4. $C_{23}H_{19}O_5S_2$ requires C, 62·0; H, 4·3%); 6-*ethoxythioindigo* (Found: S, 18·9%) (U.S.P. 1,709,982); *diacetyl-dihydro*-derivative (Found: C, 62·3; H, 4·5%). 4 : 5-*Benzthioindirubin* (Found: S, 18·3. $C_{20}H_{10}O_2S_2$ requires S, 18·6%); *diacetyl-dihydro*-derivative (Found: C, 66·5; H, 3·7. $C_{24}H_{16}O_4S_2$ requires C, 66·7; H, 3·7%): 4 : 5-*benzthioindigo* (Found: S, 18·7%) (B.P. 211,120, 233,831; D.R.-P. 466,535); *diacetyl-dihydro*-derivative (Found: C, 66·6; H, 3·9%). 5 : 6-*Benzthioindirubin* (Found: S, 18·3%); *diacetyl-dihydro*-derivative (Found: C, 66·6; H, 3·9%); 5 : 6-*benzthioindigo* (Found: S, 18·8%) (B.P. 219,280, 233,831; D.R.-P. 450,852); *diacetyl-dihydro*-derivative (Found: C, 66·4; H, 3·8%). 6 : 7-*Benzthioindirubin* (Found: S, 18·9%); *diacetyl-dihydro*-derivative (Found: C, 66·4; H, 4·0%). 6 : 7-*Benzthioindigo* (Found: S, 18·6%) (D.R.-P. 466,535); *diacetyl-dihydro*-derivative (Found: C, 66·7; H, 3·9%).

TABLE III.

Condensation of (A) 6-*Chloro*-4-*methylthionaphthenquinone* (III*b*), *and* (B) *its Anil, with the Thioindoxyls.*

Thioindoxyl		*Diacetyl-dihydro-derivatives and m. p.*	*X-Ray data.*	*Dyeing Tests.*	*Condensation.*
Thioindoxyl (I)	A	White needles, 183—184°			α
	B	„ „			
6-Chloro-4-methyl- (I*b*)	A	Colourless needles, 290—292°			α
	B	„ „			
6-Ethoxy- (I*d*)	A	Pale pink plates, 178—181°	Id.	Pale red	α
	B	„ „ „ 181—182°	„	Much deeper red	
4 : 5-Benz- (I*e*)	A	Pale brown needles, 196—198° (decomp.)		Bordeaux-red	α
	B	„ „ „ 197—199° (decomp.)		„ „	
6 : 7-Benz- (I*f*)	A	Pale brown needles, 252—253° (decomp.)			α
	B	„ „ „			
5 : 6-Benz- (I*g*)	A	Pale greenish-yellow needles, 261—263°			α
	B	„ „ „			

5 : 6′-*Dichloro*-4 : 4′-*dimethylthioindigo* (Found : S, 16·2. $C_{18}H_{10}O_2Cl_2S_2$ requires S, 16·3%) (D.R.-P. 241,910, 239,094); *diacetyl-dihydro*-derivative (Found : C, 54·8; H, 3·7. $C_{22}H_{16}O_4Cl_2S_2$ requires C, 55·1; H, 3·35%). 6′-*Chloro*-6-*ethoxy*-4′-*methylthioindigo* (Found : S, 16·7. $C_{19}H_{13}O_3ClS_2$ requires S, 16·4%) (B.P. 222,094, 232,230; U.S.P. 1,568,458); *diacetyl-dihydro*-derivative (Found : C, 57·4; H, 4·1. $C_{23}H_{19}O_5ClS_2$ requires C, 58·0; H, 4·0%). 6′-*Chloro*-4′-*methyl*-4 : 5-*benzthioindigo* (Found : S, 16·1. $C_{21}H_{11}O_2ClS_2$ requires S, 16·2%); *diacetyl-dihydro*-derivative (Found : C, 62·1; H, 3·6. $C_{25}H_{17}O_4ClS_2$ requires C, 62·5; H, 3·5%). 6′-*Chloro*-4′-*methyl*-6 : 7-*benzthioindigo* (Found : S, 16·5%); *diacetyl-dihydro*-derivative (Found : C, 62·1; H, 3·9%). 6′-*Chloro*-4′-*methyl*-5 : 6-*benzthioindigo* (Found : S, 16·6%); *diacetyl-dihydro*-derivative (Found : C, 62·4; H, 3·7%).

TABLE IV.

Condensation of (A) 5-*Chloro*-7-*methylthionaphthenquinone* (III*c*), *and* (B) *its Anil, with the Thioindoxyls.*

Thioindoxyl.		*Diacetyl-dihydro-derivatives and m. p.*	*X-Ray data.*	*Dyeing Tests.*	*Condensation.*
Thioindoxyl (I)	A	Colourless needles, 213—215°			α
	B	„ „			
5-Chloro-7-methyl- (I*c*)	A	Colourless needles, 308—310°			α
	B	„ „			
6-Ethoxy- (I*d*)	A	Colourless needles, 214—216°			α
	B	„ „			
4 : 5-Benz- (I*e*)	A	Pale brown needles, 269—272°			α
	B	„ „ „ 270—272°			
6 : 7-Benz- (I*f*)	A	Colourless needles, 167—169°	Non-id.	Pale brownish-violet	β
	B	„ „ 235—238°	„	Deep mauve	
5 : 6-Benz- (I*g*)	A	Pale greenish-yellow needles, 258—260°		Blue	α
	B	„ „ „		Blue	

5-*Chloro*-7-*methylthioindigo* (Found : S, 19·0. $C_{17}H_9O_2ClS_2$ requires S, 18·7%); *diacetyl-dihydro*-derivative (Found : C, 59·3; H, 2·8. $C_{21}H_{15}O_4ClS_2$ requires C, 59·3; H, 2·6%). 5 : 5′-*Dichloro*-7 : 7′-*dimethylthioindigo* (Found : S, 16·5. $C_{18}H_{10}O_2Cl_2S_2$ requires S, 16·3%) (D.R.-P. 241,910, 243,087); *diacetyl-dihydro*-derivative (Found : C, 55·2; H, 3·6. $C_{22}H_{16}O_4Cl_2S_2$ requires C, 55·1; H, 3·35%). 5-*Chloro*-6′-*ethoxy*-7-*methylthioindigo* (Found : S, 16·6. $C_{19}H_{13}O_3ClS_2$ requires S, 16·4%); *diacetyl-dihydro*-derivative (Found : C, 57·5; H, 4·1. $C_{23}H_{19}O_5ClS_2$ requires C, 58·0; H, 4·0%). 5′-*Chloro*-7′-*methyl*-4 : 5-*benzthioindigo* (Found : S, 16·0. $C_{21}H_{11}O_2ClS_2$ requires S, 16·2%); *diacetyl-dihydro*-derivative (Found : C, 62·2; H, 3·7. $C_{25}H_{17}O_4ClS_2$ requires C, 62·5; H, 3·5%). 5′-*Chloro*-7′-*methyl*-6 : 7-*benzthioindirubin* (Found : S, 16·5%); *diacetyl-dihydro*-derivative (Found : C, 62·2; H, 3·7%); 5′-*chloro*-7′-*methyl*-6 : 7-*benzthioindigo* (Found : S, 16·0%); *diacetyl-dihydro*-derivative (Found : C, 62·4; H, 3·7%). 5′-*Chloro*-7′-*methyl*-5 : 6-*benzthioindigo* (Found : S, 16·0%) (B.P. 251,293); *diacetyl-dihydro*-derivative (Found : C, 62·3; H, 3·3%).

TABLE V.

Condensation of (A) 6-*Ethoxythionaphthenquinone* (III*d*), *and* (B) *its Anil, with the Thioindoxyls.*

Thioindoxyl.		*Diacetyl-dihydro-derivatives and m. p.*	*X-Ray data.*	*Dyeing Tests.*	*Condensation.*
6-Chloro-4-methyl- (I*b*)	A	Pinkish plates, 138—140°	Non-id.	Very deep red	β
	B	Pale pink needles, 181—182°	„	„ „ „	
5-Chloro-7-methyl- (I*c*)	A	Pale brown plates, 148—149°			β
	B	Colourless needles, 213—215°			
6-Ethoxy- (I*d*)	A	Pale pink needles, 144—146°		Pale orange	β
	B	Pale brown crystals, 230—232°		Intense orange	
6 : 7-Benz- (I*f*)	A	Brown plates, 166—169°		Very pale mauve	β
	B	Pale pink needles, 205—208°		Mauve	
5 : 6-Benz- (I*g*)	A	Not formed			β
	B	Pale yellow plates, 224—225° (decomp.)			

6-*Chloro*-6′-*ethoxy*-4-*methylthioindirubin* (Found : S, 16·7. $C_{19}H_{13}O_3ClS_2$ requires S, 16·4%); *diacetyl-dihydro*-derivative (Found : C, 57·6; H, 4·1. $C_{23}H_{19}O_5ClS_2$ requires C, 58·0; H, 4·0%). 5-*Chloro*-6′-*ethoxy*-7-*methylthioindirubin* (Found : S, 16·6%); *diacetyl-dihydro*-derivative (Found : C, 57·5; H, 4·2%). 6 : 6′-*Diethoxythioindirubin* (Found : S, 16·9. $C_{20}H_{16}O_4S_2$ requires S, 16·6%); *diacetyl-dihydro*-derivative (Found : C, 61·0; H, 4·9. $C_{24}H_{20}O_6S_2$ requires C, 61·3; H, 4·7%) : 6 : 6′-*diethoxythioindigo* (Found : S, 16·6%) (D.R.-P. 237,680, 239,089—91); *diacetyl-dihydro*-derivative (Found : C, 61·1; H, 4·8%). 6′-*Ethoxy*-6 : 7-*benzthioindirubin* (Found : S, 16·1. $C_{22}H_{14}O_2S_2$ requires S, 16·4%); *diacetyl-dihydro*-derivative (Found : C, 67·4; H, 3·8. $C_{26}H_{20}O_5S_2$ requires C, 67·7; H, 3·6%) : 6′-*ethoxy*-6 : 7-*benzthio*-

indigo (Found: S, 16·7%); *diacetyl-dihydro*-derivative (Found: C, 67·3; H, 3·7%). *6′-Ethoxy-5 : 6-benzthioindirubin* (Found: S, 16·6%); *diacetyl-dihydro*-derivative (Found: C, 67·7; H, 3·7%): *6′-ethoxy-5 : 6-benzthioindigo* (Found: S, 16·1%); *diacetyl-dihydro*-derivative (Found: C, 67·3; H, 3·7%).

TABLE VI.

Condensation of (A) *4 : 5-Benzthionaphthenquinone* (IIIe), *and* (B) *its Anil, with the Thioindoxyls.*

Thioindoxyl.		*Diacetyl-dihydro-derivatives and m. p.*	*X-Ray data.*	*Dyeing Tests.*	*Condensation.*
Thioindoxyl (I)	A	Pale brown needles, 214—217°	Id.	Bordeaux-red	α
	B	" " "	"	" "	
6-Chloro-4-methyl- (I*b*)	A	Pale brown needles, 196—198° (decomp.)			α
	B	" " "			
5-Chloro-7-methyl- (I*c*)	A	Yellow-brown needles, 274—276°			α
	B	" "			
6-Ethoxy- (I*d*)	A	Yellowish plates, 221—224°			α
	B	" " 223—225°			
4 : 5-Benz- (I*e*)	A	Pale brown needles, >315°	Id.	Brown	α
	B	" " "	"		
6 : 7-Benz- (I*f*)	A	Pale brown needles, 255—257°		Pale brownish-violet	α
	B	" " " 254—257°		Brownish-violet	
5 : 6-Benz- (I*g*)	A	Greenish-yellow plates, 263—265°			α
	B	" "			

6′-Ethoxy-4 : 5-benzthioindigo (Found: S, 16·7. $C_{22}H_{14}O_3S_2$ requires S, 16·4%); *diacetyl-dihydro*-derivative (Found: C, 67·3; H, 3·9. $C_{26}H_{20}O_5S_2$ requires C, 67·7; H, 3·6%). *4 : 5 : 4′ : 5′-Dibenzthioindigo* (Found: S, 16·1. $C_{24}H_{12}O_2S_2$ requires S, 16·2%) (D.R.-P. 239,094); *diacetyl-dihydro*-derivative (Found: C, 69·5; H, 4·1. $C_{28}H_{16}O_4S_2$ requires C, 69·7; H, 3·7%). *4 : 5 : 6′ : 7′-Dibenzthioindigo* (Found: S, 16·4%); *diacetyl-dihydro*-derivative (Found: C, 69·5; H, 4·2%). *4 : 5 : 5′ : 6-Dibenzthioindigo* (Found: S, 16·5%); *diacetyl-dihydro*-derivative (Found: C, 69·7; H, 3·6%).

TABLE VII.

Condensation of (A) *6 : 7-Benzthionaphthenquinone* (IIIf), *and* (B) *its Anil, with the Thioindoxyls.*

Thioindoxyl.		*Diacetyl-dihydro-derivatives and m. p.*	*X-Ray data.*	*Dyeing Tests.*	*Condensation.*
Thioindoxyl (I)	A	Colourless needles, 254—256°			α
	B	" "			
5-Chloro-7-methyl- (I*c*)	A	Colourless needles, 235—238°			α
	B	" "			
6-Ethoxy- (I*d*)	A	Pale pink plates, 162—165°		Dull brown-red	β
	B	Pale pink needles, 205—208°		" " "	
4 : 5-Benz- (I*e*)	A	Pale brown plates, 227—230° *		Dark brown	β
	B	Pale brown needles, 255—257° *		" "	
6 : 7-Benz- (I*f*)	A	Colourless plates, >315°	Id.	Brown	α
	B	" "	"	"	
5 : 6-Benz (I*g*)	A	Pale green plates, 251—253°	Id.		α
	B	" " " 252—253°	"		

* Mixed m. p. 215—223°.

Ethoxy-6′ : 7′-benzthioindirubin (Found: S, 16·7. $C_{22}H_{14}O_3S_2$ requires S, 16·4%); *diacetyl-dihydro*-derivative (Found: C, 67·5; H, 3·6. $C_{26}H_{20}O_5S_2$ requires C, 67·7; H, 3·6%). *4 : 5 : 6′ : 7′-Dibenzthioindirubin* (Found: S, 16·5. $C_{24}H_{12}O_2S_2$ requires S, 16·2%); *diacetyl-dihydro*-derivative (Found: C, 69·5; H, 3·7. $C_{28}H_{16}O_4S_2$ requires C, 69·7; H, 3·7%). *6 : 7 : 6′ : 7′-Dibenzthioindigo* (Found: S, 16·4%) (D.R.-P. 239,093); *diacetyl-dihydro*-derivative (Found: C, 69·6; H, 3·9%). *5 : 6 : 6′ : 7′-Dibenzthioindigo* (Found: S, 16·5%) (D.R.-P. 519,747); *diacetyl-dihydro*-derivative (Found: C, 69·3; H, 3·9%).

TABLE VIII.

Condensation of (A) *5 : 6-Benzthionaphthenquinone* (IIIg), *and* (B) *its Anil, with the Thioindoxyls.*

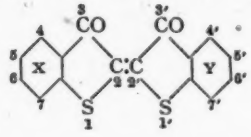
Thioindoxyl.		*Diacetyl-dihydro-derivatives and m. p.*	*X-Ray data.*	*Dyeing Tests.*	*Condensation.*
Thioindoxyl (I)	A	Not formed (p. 407)			β
	B	Pale green plates, 254—256°			
5-Chloro-7-methyl- (I*c*)	A	Not formed			β
	B	Pale greenish-yellow needles, 258—260°			
6-Ethoxy- (I*d*)	A	Not formed			β
	B	Pale yellow plates, 224—225° (decomp.)			
4 : 5-Benz- (I*e*)	A	Not formed		Pale fawn	β
	B	Greenish-yellow needles, 263—265°		Mauve	
6 : 7-Benz- (I*f*)	A	Not formed	Non-id.	Very pale mauve	β
	B	Greenish-brown plates, 251—253°	"	Deep violet	
5 : 6-Benz- (I*g*)	A	Not formed		Pale bluish-green	β
	B	Pale green needles, 297—300° (decomp.)		Dark greenish-blue	

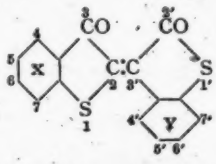
5-Chloro-7-methyl-5′ : 6′-benzthioindirubin (Found: S, 16·3. $C_{21}H_{11}O_2ClS_2$ requires S, 16·2%). *6-Ethoxy-5′ : 6′-benzthioindirubin* (Found: S, 16·6%). *4 : 5 : 5′ : 6′-Dibenzthioindirubin* (Found: S, 16·0%). *6 : 7 : 5′ : 6′-Dibenzthioindirubin* (Found: S, 16·5%). *5 : 6 : 5′ : 6′-Dibenzthioindirubin* (Found: S, 16·5%); *5 : 6 : 5′ : 6′-dibenzthioindigo* (Found: S, 16·5%) (B.P. 219,280); *diacetyl-dihydro*-derivative (Found: C, 70·0; H, 3·9%).

Each table gives the reactions of one thioquinone (A) and its α-anil (B) with each of the thioindoxyls studied. The third column gives the m. p.'s of the diacetyl-dihydro-derivatives: when these were identical for a pair of derivatives, their chemical identity was always confirmed by mixed m. p. determinations. The *X*-ray data in the fourth column are given as Id. = identical, and Non-id. = non-identical. The last column (Type of Condensation) indicates the particular carbonyl group of the thioquinone which has reacted: the reference compound obtained from the α-anil (B) is always the α-condensation product.

The names and analytical data of all new compounds are given below each table in the order in which they appear. In all cases, unless otherwise stated, nitrobenzene has been used as a recrystallising solvent for the dye and acetic acid for the diacetyl-dihydro-derivatives.

The thioindigos and thioindirubins are named according to (XXXIV) and (XXXV) respectively.

(XXXIV.) 

 (XXXV.)

Condensation Products of Indoxyl and the Thionaphthenquinones.—In this series, the direct comparison in properties of (A) the compounds obtained by the condensation of indoxyl with the quinones, and (B) the reference compounds prepared by the condensation of isatin chloride with the required thioindoxyl, cannot be conveniently tabulated, as the compounds were identified by their alkali fission products, the aldehydes so obtained being identified sometimes as free aldehydes and sometimes (when this proved difficult) as their phenylhydrazones. The two series (A) and (B) differed throughout, the (B) series being necessarily 2-thionaphthen-2′-indole-indigos (XII) giving substituted thio-indoxyl-2-aldehydes (XVI) (p. 407), and the (A) series being therefore 3-thionaphthen-2′-indole-indigos (XIV) giving substituted thio-oxindole-3-aldehydes (XV). The compounds and their derivatives in each series are therefore given separately. Since the difference between the two series was manifest, standard dyeing tests were not made, and the colour of the crystalline dye is therefore recorded. General dyeing tests showed, however, that both series (A) and (B) formed good dyes. All the dyes in (A) and (B) were recrystallised from nitrobenzene, and the aldehydes and their phenylhydrazones from dilute alcohol.

(A) Indoxyl condensed with: (i) the quinone (III) gives the indigo (XIV), which on alkali fission gives the aldehyde (XV): this was shown by Friedländer (*loc. cit.*) and was therefore not repeated.

(ii) the quinone (III*b*) gave 3-(6-*chloro*-4-*methylthionaphthen*)-2′-*indole-indigo*, reddish-violet plates (Found: S, 9·9. $C_{17}H_{10}O_2NClS$ requires S, 9·7%), which gave 6-*chloro*-4-*methylthio-oxindole*-3-*aldehydephenylhydrazone*, m. p. 167—169° (Found: C, 61·1; H, 4·4; N, 8·7. $C_{16}H_{13}ON_2ClS$ requires C, 60·8; H, 4·1; N, 8·85%).

(iii) the quinone (III*c*) gave the corresponding 3-(5-*chloro*-7-*methyl*) derivative, violet plates (Found: S, 10·0%), which gave the 5-*chloro*-7-*methyl*-*aldehyde*, m. p. 116—118° (Found: C, 52·6; H, 3·5. $C_{10}H_7O_2ClS$ requires C, 53·0; H, 3·1%), *phenylhydrazone*, m. p. 194—196° (Found: C, 60·4; H, 4·2; N, 8·9%).

(iv) the quinone (III*d*) gave the 3-(6-*ethoxy*)-derivative, reddish-violet plates (Found: S, 10·2. $C_{18}H_{13}O_3NS$ requires S, 9·9%), which gave the 6-*ethoxy*-*aldehyde*, m. p. 152—154° (Found: C, 59·1; H, 4·6. $C_{11}H_{10}O_3S$ requires C, 59·5; H, 4·5%).

(v) the quinone (III*e*) gave the 3-(4 : 5-*benz*)-derivative, dark blue plates (Found: S, 9·4. $C_{20}H_{11}O_2NS$ requires S, 9·7%) (E.P. 189,782), which gave the 4 : 5-*benz*-*aldehyde*, m. p. 144—145° (Found: C, 68·6; H, 3·5. $C_{13}H_8O_2S$ requires C, 68·4; H, 3·5%).

(vi) the quinone (III*f*) gave the 3-(6 : 7-*benz*)-derivative, dark blue-violet plates (Found: S, 10·0%), which gave the 6 : 7-benz-aldehyde, identified as the *phenylhydrazone*, m. p. 220—222° (Found: C, 71·4; H, 4·7. $C_{19}H_{14}ON_2S$ requires C, 71·7; H, 4·4%).

(vii) the quinone (III*g*) gave the 3-(5 : 6-*benz*)-derivative, dark blue-violet plates (Found: S, 10·1%), which gave the 5 : 6-*benz*-*aldehyde*, m. p. 145—146° (Found: C, 68·9; H, 3·7%).

(B) Isatin chloride condensed with: (i) thioindoxyl (I) gives the indigo (XII), which on alkali splitting gives the aldehyde (XVI): this was also shown by Friedländer and was not repeated.

(ii) the thioindoxyl (I*b*) gave 2-(6-*chloro*-4-*methylthionaphthen*)-2′-*indole-indigo*, violet crystals (Found: S, 10·1%), which gave 6-*chloro*-4-*methylthioindoxyl*-2-*aldehydephenylhydrazone*, m. p. 153—154° (Found: C, 60·6; H, 4·3%).

(iii) the thioindoxyl (I*c*) gave the corresponding 2-(5-*chloro*-7-*methyl*) derivative, deep blue plates (Found: S, 10·0%).

(iv) the thioindoxyl (I*d*) gave the 2-(6-*ethoxy*)-derivative, reddish-violet plates (Found: S, 10·2%).

(v) the thioindoxyl (I*e*) gave the 2-(4 : 5-*benz*)-derivative, reddish-violet plates (Found: S, 9·4%) (B.P. 233,831), which gave the 4 : 5-*benz*-*aldehyde*, m. p. 131—132° (Found: C, 68·2; H, 3·5%).

(vi) the thioindoxyl (I*f*) gave the 2-(6 : 7-*benz*)-derivative, deep blue plates (Found: S, 10·0%) (E.P. 233,831), which gave the 6 : 7-benz-aldehyde, identified as the *phenylhydrazone*, m. p. 197—200° (Found: C, 71·9; H, 4·6%).

(vii) the thioindoxyl (I*g*) gave the 2-(5 : 6-*benz*)-derivative, deep blue-violet plates (Found: S, 10·1%) (D.R.-P. 490,599; U.S.P. 1,709,982), which gave the 5 : 6-*benz*-*aldehyde*, m. p. 137—139° (Found: C, 68·1; H, 3·6%).

All attempts to prepare aldehydes by the alkali-splitting of the dyes in B (iii) and B (iv) above were unsuccessful, only highly-coloured alkali-soluble products being obtained.

Condensation Products of Oxindole and the Thionaphthenquinones.—In this series, (A) the compounds produced from the condensation of oxindole with the quinones, and (B) the reference compounds obtained either by the condensation of isatin with the thioindoxyls or by oxindole with the anils, were found throughout to be identical by *X*-ray investigation. Alkali splitting of the product (type XIII), to furnish the oxindole-3-aldehyde (XVII) (p. 407) was rarely used because of its difficulty. All the compounds produced in this series are therefore 2-thionaphthen-3′-indole-indigos: in the following list, the first analytical figure given refers to the product obtained in (A) and the second to that in (B).

(i) 2-Thionaphthen-3′-indole-indigo, red needles (D.R.-P. 182,260, 241,327).

(ii) 2-(6-*Chloro*-4-*methylthionaphthen*)-3′-*indole-indigo*, red needles (Found: S, 9·3. $C_{17}H_{10}O_2NClS$ requires S, 9·7%).

(iii) the 2-(5-*chloro*-7-*methyl*) derivative, reddish needles (Found: S, 10·0, 10·1%).

(iv) the 2-(6-*ethoxy*)-derivative, red needles (Found: S, 9·6, 10·1. $C_{18}H_{13}O_2NS$ requires S, 9·9%).

(v) the 2-(4 : 5-*benz*)-derivative, dark brown needles (Found: S, 10·1, 9·7. $C_{20}H_{11}O_2NS$ requires S, 9·7%) (B.P. 198,415).

(vi) the 2-(6 : 7-benz)-derivative, dark brown needles (Found: S, 9·3, 9·8%) (Dutta, *Ber.*, 1933, **66**, 1230).

(vii) the 2-(5 : 6-benz)-derivative, violet-brown plates (Found: S, 10·1, 9·9%) (Dutta, *Ber.*, 1934, **67**, 1324).

2-*Acetamido*-1-*naphthylthioglycollic Acid* (XXX).—Acetic anhydride (40 c.c.; 2 mols.) was added dropwise with

stirring to a solution of the sodium salt of the acid (XXIX) (100 g., 85% pure) in water (300 c.c.). Stirring was continued for 1 hour, during which much grey precipitate formed, and then 10% sodium hydroxide solution (350 c.c.) was slowly added, and the solution filtered from traces of the amino-acid lactam. The filtrate on acidification gave the *acid* (XXX), long colourless needles (alcohol), m. p. 185° (Found: C, 61·4; H, 4·8; N, 5·2. $C_{14}H_{13}O_3NS$ requires C, 61·1; H, 4·7; N, 5·1%). The addition of the sodium hydroxide in this preparation is essential, otherwise the final product (XXX) is heavily contaminated with the acid-lactam.

Attempted cyclisation. The directions given in the D.R.-P. 414,084 (addition of the acid to chlorosulphonic acid in the absence of solvent) gave only the thioindigo and sulphonated products. The same result was obtained with chlorosulphonic acid (1—4 mols.) in tetrachloroethane as solvent and it seems that, although the required thioindoxyl is formed, it is impossible to prevent oxidation and sulphonation occurring.

2-*Chloro*-1-*naphthylthioglycollic Acid.*—A solution of the crude sodium salt of the amino-acid (XXIX) (100 g.) and sodium nitrite (25 g.) in water (300 c.c.) was run into a mixture of ice (300 g.) and concentrated hydrochloric acid (200 c.c.), and this solution in turn added to a solution of cuprous chloride (50 g.) in concentrated hydrochloric acid (200 c.c.) at 70°; a brown oil separated. The temperature was then increased to 90° for 1 hour, and the mixture finally cooled, the brown oil solidifying. The aqueous solution was decanted from the sticky brown solid, which was dissolved in hot 5% sodium hydroxide solution. The latter was filtered and cooled, and the sodium salt of the chloro-acid salted out, collected, and partly purified by recrystallisation from 15% brine. The *chloro-acid* was precipitated by the addition of hydrochloric acid to a chilled aqueous solution of this sodium salt, and obtained as a sticky product which solidified. It was recrystallised thrice from dilute alcohol (charcoal) and once from benzene–*cyclo*hexane, forming colourless crystals (19 g.), m. p. 95—97° (Found: C, 57·2; H, 3·7; Cl, 13·8. $C_{12}H_9O_2ClS$ requires C, 57·2; H, 3·5; Cl, 14·1%).

Attempted cyclisation. Chlorosulphonic acid (9 g.; 1·5 mols.) was added dropwise to a well-stirred suspension of the acid (13 g.) in tetrachloroethane (50 c.c.) at 0—5°. After 2 hours, water was added, and the tetrachloroethane removed in steam. The sticky brown residue was almost completely soluble in hot sodium carbonate solution and was unaffected by potassium ferricyanide. It was therefore the unchanged acid. The same result was obtained when the acid (10 g.) was added in small portions to chlorosulphonic acid (20 g.) with stirring at 0°, though in this case a small amount of the blue thioindigo was also obtained. An attempt at cyclisising the acid chloride (XXXIII) with aluminium chloride, as in the preparation of 5-chloro-7-methylthioindoxyl, was equally unsuccessful, the only product obtained being the impure thioindigo.

In view of the considerable value of diacetyl-dihydro-derivatives for the rapid identification of the parent thioindigos and thioindirubins, the m. p.'s of the derivatives described above are collected in Table IX. The benzene rings in each molecule are differentiated as X and Y, according to formulæ (XXXIV) and (XXXV). In the columns headed "Thioindirubin derivative," a blank space indicates that the parent thioindirubin has not been obtained in this investigation, and "n.f." indicates that the thioindirubin has been obtained but does not form a diacetyl-dihydro-derivative.

TABLE IX.

M. p.'s of Diacetyl-dihydro-derivatives of Thioindigos and Thioindirubins.

Substitution. X.	Y.	Thioindigo derivative.	Thioindirubin derivative.	Substitution. X.	Y.	Thioindigo derivative.	Thioindirubin derivative.
—	—	248°	148—149°	5-Cl-7-Me	4 : 5-Benz	274—276°	
6-Cl-4-Me	—	183—184	144—145	,,	5 : 6-Benz	258—260	n.f.
5-Cl-7-Me	—	213—215		6-OEt	6-OEt	230—232	144—146°
6-OEt	—	162—165	131—133	,,	4 : 5-Benz	223—225	
4 : 5-Benz	—	214—217	162—163	,,	5 : 6-Benz	224—225	n.f.
5 : 6-Benz	—	254—256	n.f.	,,	6 : 7-Benz	205—208	162—165
6 : 7-Benz	—	254—256	178—179	6 : 7-Benz	5-Cl-7-Me	235—238	167—169
6-Cl-4-Me	6-Cl-4-Me	290—292		,,	6-OEt	205—208	166—169
5-Cl-7-Me	5-Cl-7-Me	308—310		4 : 5-Benz	4 : 5-Benz	>315	
6-Cl-4-Me	6-OEt	181—182	138—140	,,	5 : 6-Benz	263—265	n.f.
,,	4 : 5-Benz	197—199		,,	6 : 7-Benz	255—257	227—230
,,	5 : 6-Benz	261—263		5 : 6-Benz	5 : 6-Benz	297—300	n.f.
,,	6 : 7-Benz	252—253		6 : 7-Benz	6 : 7-Benz	>315	
5-Cl-7-Me	6-OEt	214—216	148—149	,,	5 : 6-Benz	252—253	n.f.

This Table shows that symmetric substitution in the thioindigo derivatives is associated with high m. p.; *e.g.*, the 4 : 5 : 4′ : 5′-dibenz-derivative has a higher m. p. than the isomeric unsymmetric 4 : 5 : 5′ : 6′- and 4 : 5 : 6′ : 7′-derivatives.

We are greatly indebted to Dr. W. H. Taylor and Dr. A. Hargreaves for the *X*-ray analyses, and to I.C.I. (Dyestuffs) Ltd. for a grant and for materials.

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NOTE.

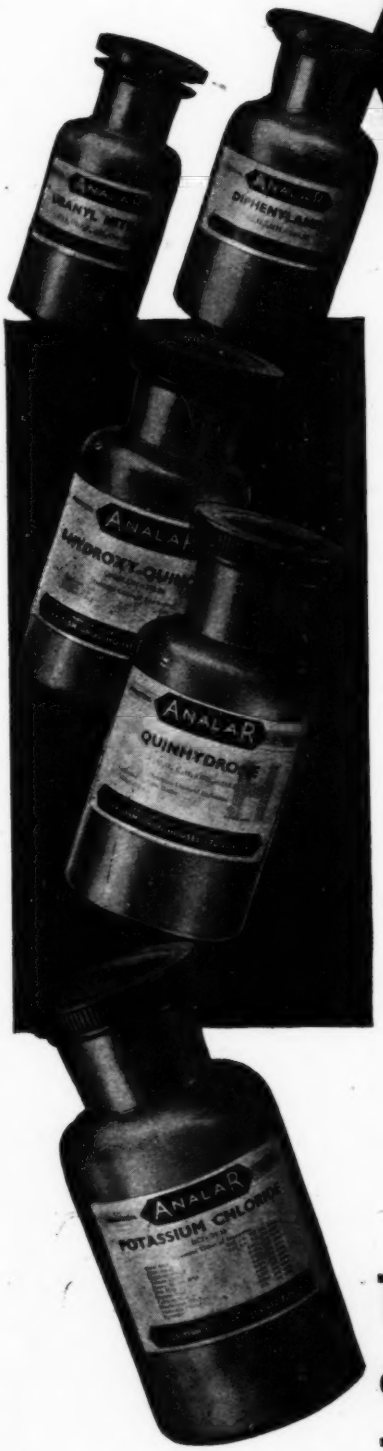
A Preparation of 8-*Hydroxyquinoline.* By F. E. KING and J. A. SHERRED.

8-METHOXYQUINOLINE, obtained by Skraup (*Monatsh.*, 1882, **3**, 544) from *o*-anisidine and glycerol in presence of 2-nitroanisole, has been prepared with arsenic pentoxide as oxidising agent. Its demethylation, previously effected by aniline hydrochloride under pressure (Riedel, D.R.-P. 583,705), in nearly quantitative yield, simply with boiling hydrobromic acid, is now described.

8-*Methoxyquinoline.*—Concentrated sulphuric acid (100 g.) was cautiously added to a mixture of redistilled *o*-anisidine (44·5 g.), arsenic pentoxide (51·5 g.), and glycerol (110 g.), and the moderate reaction initiated by heating under reflux. After 4 hours' boiling, the liquid was diluted with water to 1 l. and made slightly alkaline with concentrated aqueous sodium hydroxide. The precipitated oil was separated and distilled. The main fraction, b. p. 174—176°/29 mm. (yield 27%), was the pure methoxyquinoline, m. p. 45°, of which the picrate, crystallised from alcohol and dried in a

vacuum, had m. p. 162° (Found: C, 49·4; H, 3·1. Calc.: C, 49·5; H, 3·1%). Fränkel and Grauer (*Ber.*, 1913, **46**, 2552) give m. p. 143° (decomp.) with discolouration at 130°.

8-*Hydroxyquinoline.*—A solution of the methoxyquinoline (5 g.) in hydrobromic acid (30—40 c.c.; *d* 1·5) was refluxed in glass-jointed apparatus for 3—4 hours. Crude 8-hydroxyquinoline could then be precipitated by solid sodium carbonate, or the acid first recovered by evaporation under diminished pressure. The phenolic base was liberated from the viscous hydrobromide by approximately the calculated amount of carbonate solution and distilled (yield, above 90%); b. p. 122°/0·1 mm., m. p. 77°. As recorded by Skraup (*loc. cit.*), the picrate crystallised in yellow prisms, sintering *ca.* 170°, m. p. 203—204° (Found: C, 48·1; H, 2·7. Calc.: C, 48·1; H, 2·7%).—DYSON PERRINS LABORATORY, OXFORD. [*Received, September 5th*, 1941.]



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